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A STUDY OF BRAIN REPAIR IN THE RAT BY THE USE OF TRYPAN BLUE

WITH SPECIAL REFERENCE TO THE VITAL STAINING OF THE MACROPHAGES *

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Not a little light has been shed on certain of the phagocytic cells found in areas of aseptic inflammation by the use, in histophysiologic investigations, of the so-called "vital-dyes," and particularly by the employment of the azo dyes of the benzidin series. Tschaschin [1] produced lesions of lymph glands, liver and spleen by burning with a red-hot needle, and introduced trypan blue, and other similar substances, into the circulating fluids of the animals during the period of repair. He showed that the mononuclear phagocytes, which throng the inflamed tissues around these lesions, rapidly became filled with large quantities of the dyestuff, held in the form of numberless minute granules or droplets. Other workers have noted similar phenomena, and it is generally recognized now that these mononuclear phagocytic cells, during a certain period of their existence at least, take up such dyes from the surrounding fluids with avidity, and store them in the cytoplasm. C. C. Macklin[2] has recently studied the inflammatory reaction consequent on injuries of bone in rats which were vitally stained with trypan blue shortly before being killed. He found that, in the tissues immediately surrounding the injured bone (fractured ribs, tibias and femora, and trephined skulls), the dye-containing phagocytes were very abundant and large in stages ranging from the second to the tenth days or later, and he concluded that their mobilization in this region was for the purpose of assisting in the removal of the waste material, the result of the injury.

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1. Tschaschin, S.: Ueber die "ruhenden Wanderzellen" und ihre Bezeihungen zu den anderen Zellformen des Bindegewebes und zu den Lymphozyten, Fol. Haematol. **17**:317, 1913.

2. Macklin, C. C.: Bone-Repair in the Rat Vitally Stained with Trypan Blue, Anat. Record **14**:43, 1918. The Development and Function of Macrophages in the Repair of Experimental Bone-Wounds in Rats Vitally Stained with Trypan-Blue, Publication 272, Carnegie Institution of Washington, Contributions to Embryology, No. 27, p. 1, 1919.

These phagocytes of aseptic inflamed tissues are quite comparable to the similar cells which are always found scattered throughout the body under normal conditions and which, though differing morphologically among themselves, yet possess in common a phagocytic potentiality toward "finely particulate matter" which has led to their being grouped under the physiologic term "macrophage" by Evans.[3] The macrophages of inflammation, however, are as a rule more numerous, larger and their phagocytic powers seem to be enhanced.

The vital dye taken up by the macrophages renders them easily visible, and also indicates their phagocytic function, for the view is commonly held that the taking up of the ultramicrons of the colloidal dyestuffs from the surrounding fluids, and the storage of these particles within the cytoplasm in the form of small droplets or granules, is a process analogous to that of the phagocytosis of particulate matter (Evans[3] et al.). The physiologic significance of the reaction of these cells to vital dyes has recently been discussed by Shipley.[4]

Although there is no undisputed theory of the origin of these cells, it seems probable from a review of the numerous articles which have appeared on the subject (in particular some of those of Maximow) that, in areas of aseptic inflammation, such as those mentioned above, the macrophages are recruited from several sources, such as the clasmatocytes of the local tissues, the endothelial cells, certain reticulum cells (such as those of the bone marrow, spleen and lymph glands), the tissue lymphocytes and, in some cases perhaps most abundantly of all, from certain lymphocytoid cells of the blood strained out of the current by the peculiar structural and physical conditions of the inflammatory area.

The work on bone wounds suggested the carrying out of similar experiments on brain tissue, for it has long been known that, in injured brain, large mononuclear phagocytes soon appear and become a conspicuous feature of the repair process; and it appeared more than probable that these cells would show an ability to take up and store the vital dyestuffs. Indeed, MacCurdy and Evans,[5] by injecting trypan-blue into monkeys which were the subjects of experimental poliomyelitis, found that cells (Körnchenzellen, endothelial cells, etc.), staining vitally with these dyes, were present in the brain lesions. They regard the Körnchenzellen as typical macrophages (Evans[3]).

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3. Evans, H. M.: The Macrophages of Mammals, Am. J. Physiol. **37**:243, 1915.

4. Shipley, P. G.: The Physiological Significance of the Reaction of Tissue Cells to Vital Benzidine Dyes, Am. J. Physiol. **49**:284, 1919.

5. MacCurdy, J. T., and Evans, H. M.: Experimentelle Läsionen des Centralnervensystems, untersucht mit Hilfe der vitalen Färbung, Berl. klin. Wchnschr. **49**:1695, 1912.

The brain is a particularly favorable field for the employment of this method, since the tissue is white and contrasts well with the dye; and since it contains no cells (except in the hypophysis and choroid plexus) which under normal conditions takes the dye (Goldmann[6] et al.). Thus any dye which would be taken up in the inflammatory area in the brain would be very conspicuous.

The animal selected was the rat, since it is easily obtained, conveniently handled, and had already been used in the bone experiments. Moreover, the brain is small, and may be removed without trouble. Both albinos and crossed black and white animals were used. They were all healthy, young, and well developed. We obtained them from the excellent colony of the School of Hygiene and Public Health of Johns Hopkins University.

In the principal series (S27) the injury was produced (under ether anesthesia) by plunging an ordinary dissecting needle, heated to redness in the flame of a Bunsen burner, into the depths of the cerebrum, a small hole having first been bored in the skull through the midparietal area, after reflection of the shaved scalp. The needle was withdrawn at once, the tissue not being exposed, as a rule, for more than one-half second. However, there was naturally some variation in the time of exposure. In the first few experiments, too, a slender needle was employed, which produced a slighter injury than that made by the coarser needle used later. Thus the injuries were not absolutely uniform in degree, but this was of little or no importance from the standpoint of the object of the experiments. The hot needle-stab has been used to produce experimental brain injuries by a number of workers, such as Coen,[7] Tschistowitsch[8] and others. Aseptic technic was observed and, with two exceptions (one of which was discarded and the other, S27-41, classed as an abscess) there was no resulting infection. Several animals were killed by the operation, but the survivors showed a very low mortality. A uniform technic of staining was carried out, each animal receiving intraperitoneally 4 or 5 c.c. of a 1 per cent. aqueous solution of Grübler's trypan blue forty-eight hours before being sacrificed, followed by a second dose after twenty-four hours. In those animals which were killed sooner than forty-eight hours after the operation the same procedure was carried out, the dye being given at the proper intervals before the operation. In a few of these cases (shown in the table), at the time

6. Goldmann, E. E.: Vitale Färbung und Chemotherapie, Berl. klin. Wchnschr. **49**:1689, 1912.

7. Coen, E.: Ueber die Heilung von Stichwunden des Gehirnes, Beiträge zur pathol. Anat. u. Physiol. (Ziegler) **2**:107, 1887.

8. Tschistowitsch, T.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beiträge zur pathol. Anat. u. zur allgem. Pathol. (Ziegler) **23**: 321, 1898.

of the operation, an additional dose of 1 or 2 c.c. was given. In only two cases did the total dose ever exceed 10 c.c. of dye. Some slight variations from this technic occurred, as shown in the table.

The animals were usually killed by rapidly washing out the blood vessels of the brain with warm saline, under chloroform anesthesia, after which a 10 per cent. aqueous solution of liquor formaldehydi was run through for about thirty minutes. In some cases the preliminary washing with saline was omitted and a few cases were fixed by immersion, but those from whose vessels the blood had been washed afforded a much clearer picture of the staining. The brain was then dissected out and hardened in liquor formaldehydi.

The stages examined ranged from the time of injury to the seventy-fourth day, and forty-four animals were used in Series 27. These represented twenty-four stages of repair. Almost all brains were examined in liquor formaldehydi in the gross and with the binocular, both as a whole and split transversely so as to show the longitudinal aspects of the stab. Sketches and full notes were made of the results of these observations at the time, and in every brain used. Most of the brains were then cleared in oil of wintergreen and examined with the binocular microscope. Sections of twenty-four cases, extending through the series, were cut from paraffin blocks, usually so as to show the entire length of the stab, at thicknesses varying from 5 to 15 microns. The thin sections were usually mounted clear, or stained lightly with carmin. Hematoxylin and eosin were often used, and, in special cases, tinctorial reactions were obtained for iron, connective tissue, neuroglia, etc. A few brains, with lesions such as those described, at different stages, were immersed for several days in a fixing solution containing osmic acid, and afterward cut into sections for the study of fat.

For low power work, sections of 25, 50 and even 100 microns were made; these were cleared and mounted without conterstaining, and were used in studying the grosser features of the dye distribution.

A number of brains from additional animals operated on in the same manner were examined in the fresh condition, the tissues of the lesion being carefully teased out in Locke's solution and examined as they were, for the study of the vital staining; or treated with a fat stain, as sudan III or Nile blue sulphate. The teasing method, with the use of fat stains, was resorted to in formaldehyd fixed material as well, and gave some interesting results, as did also frozen sections of such material. An interpretation of any one stage was based on the picture gained from the use of all these methods.

As a vital dye, Niagara blue 3B (No. 46159, National Aniline and Chemical Co.) was used in one case (S27-35, two and one-half hour stage) in two doses of 5 c.c. each, the solution being rather stronger than 1 per cent. The staining was for twenty-four hours. It was

more toxic than trypan blue, causing depression. Three other rats, injected with the same solution at the same time, were found dead the next morning.

In a tentative experiment, Niagara blue 2B (same manufacturer) was given in a 4 c.c. dose of 1 per cent. strength. The animal was killed at the end of two days, after twenty-four hours of staining. This dye also was more toxic than trypan blue.

Additional experiments, using nineteen animals, were carried out, in which the operative technic was varied somewhat. In two cases a cold needle was used instead of a hot one. In nine others the hole in the brain, made either by burning or by cutting out with a cold sterile scalpel, was filled with sterile muscle, liver or spleen. Again, in three cases the injury was accomplished by inflicting a sharp blow on the head with the end of a small nail, driven into a wooden handle. This produced either a simple concussion or a depressed fracture, depending on the strength of the blow and the thickness of the skull. In these cases the vital staining procedure was usually the same as in S27; all departures from it are noted. Prolonged staining from the time of operation was tried in two cases, and in two cases (in addition to some of the fresh material) the hot stab operation was done without staining.

The table of material contains a list of these cases. It does not include the fresh material.

TABLE OF MATERIAL

Experiment	Stage	Number	Staining		Sections Prepared	Remarks
			Amount, C.c.	Duration, Hours		
I. Hot stabs, vitally stained	0 hours	S27-11	4	24	No	
	0 hours	S27-12	4	24	No	
	1 hour	S27-26	8	48	No	Weakly stained
	1 hour	S27-32	8	48	No	1 c.c. dye, intravenously at operation
	2½ hours	S27-27	8	48	Yes	
	2½ hours	S27-33	8	48	No	2 c.c. dye, intraperitoneally at operation
	2½ hours	S27-35	10	24	Yes	Niagara blue, 3B, 1+ %
	4 hours	S27-28	8	48	Yes	
	4 hours	S27-34	8	48	No	2 c.c. dye, intraperitoneally at operation
	6 hours	S27-24	8	48	Yes	2 c.c. dye, intraperitoneally at operation
	6 hours	S27-25	8	48	No	2 c.c. dye, intraperitoneally at operation
	12 hours	S27-22	8	48	Yes	
	12 hours	S27-23	8	48	No	
	1 day	S27-21	8	48	No	
	1 day	S27-5	8	48	Yes	
	32 hours	S27-44	10	32	No	Died
	2 days	S27-6	8	72	Yes	
	2 days	S27-7	8	48	No	
	2 days	S27-8	8	48	Yes	
	2 days	S27-36	10	48	No	Stabs in both hemispheres
	3 days	S27-37	10	48	Yes	Slight injury
	3 days	S27-39	10	48	Yes	Severe injury
	3 days	S27-49	12	48	Yes	Also used for osmic acid preparations, and spreads of pia and dura

TABLE OF MATERIAL—(*Continued*)

Experiment	Stage	Number	Staining		Sections Prepared	Remarks
			Amount,	Duration,		
I. Hot stabs, vitally stained	4 days	S27-9	8	48	Yes	
	4 days	S27-10	8	48	No	
	5 days	S27-55	10	48	Yes	Transverse sections
	5 days	S27-56	5	24	Yes	Transverse sections
	6 days	S27-13	8	48	Yes	Slight injury
	6 days	S27-14	8	48	No	
	7 days	S27-57	10	48	Yes	Transverse sections
	8 days	S27-29	8	48	No	
	8 days	S27-58	10	48	Yes	Transverse sections
	10 days	S27-15	8	48	Yes	
	10 days	S27-16	8	48	No	
	15 days	S27-17	8	48	No	
	15 days	S27-18	8	48	Yes	
	18 days	S27-43	10	48	Yes	Also used for osmic acid preparations, and spread of dura
	20 days	S27-19	8	48	Yes	
	20 days	S27-20	8	48	No	
	24 days	S27-46	10	48	Yes	Also used for osmic acid preparations, and spreads of pia and dura
	29 days	S27-31	8	48	No	Stab in olfacory lobe
	34 days	S27-2	8	48	Yes	
	35 days	S27-1	8	48	No	
	74 days	S27-4	8	48	Yes	
	24 stages	44 cases			24 sectioned	
II. Cold stabs, vitally stained	2 days	S31-1	10	48	Yes	
	6 days	S31-2	10	48	Yes	
	2 stages	2 cases			2 sectioned	
III. Head blows, vitally stained	18 hours	S28-1	4	18	No	
	4 days	S28-2	4	24	No	Spreads of pia
	11 days	S28-3	8	48	No	
	3 stages	3 cases			No sections	
IV. Muscle insert in hole in brain, vitally stained	2 days	S29-1	10	48	Yes	
	6 days	S29-2	10	48	Yes	
	10 days	S29-3	10	48	Yes	
	3 stages	3 cases			3 sectioned	
V. Muscle insert in hot stab, vitally stained	2 days	S30-1	10	48	Yes	
	6 days	S30-2	10	48	Yes	Spreads of dura
	2 stages	2 cases			2 sectioned	
VI. Liver insert in hole in brain, vitally stained	2 days	S32-1	10	48	Yes	
	6 days	S32-2	10	48	Yes	
	2 stages	2 cases			2 sectioned	
VII. Spleen insert in hole in brain, vitally stained	2 days	S33-1	10	48	Yes	
	2 days	S33-2	3	24	Yes	
	1 stage	2 cases			2 sectioned	
VIII. Hot stabs with prolonged vital staining	11 days	S27-45	10	11 days	Yes	Spreads of pia and dura. Died
	15 days	S27-47	15	15 days	Yes	
	2 stages	2 cases			2 sectioned	
IX. Abscess formation in hot stab, vitally stained	12 days	S27-41	10	48 hours	Yes	Spreads of pia and dura
	1 stage	1 case			1 sectioned	
X. Hot stabs without vital staining	4 days	S27-52	..	..	No	Head injected through aorta with Prussian blue, and cleared for study of vessels
	62 days	S27-3	..	..	Yes	Died while dye was being injected
	2 stages	2 cases			1 sectioned	

GROSS PATHOLOGY

The main line of the description will follow along Series 27, and digressions will be made from time to time to discuss the results of the special experiments. Let us consider first the appearance of a typical, vitally stained brain from Series 27. Such a brain presents a characteristic picture (Fig. 1, twelve-hour stage, and Fig. 2, six-day stage). The injured region is very conspicuous, being intensely blue, in contrast to the normal color of the rest of the brain. In the center the needle-stab appears as a dark blue spot.

On examination with the binocular microscope the center of this blue area, usually from 1 to 3 mm. across, is seen to be irregular, somewhat depressed, and typically of a dark grayish blue. It represents the seared and coagulated brain substance; we have termed it the "coagulum." Almost always the upper part adheres to the dura, and on being separated, an irregular surface is left. The coagulum has shrunk away from its surroundings during the process of its formation, and thus we find it enclosed by a narrow, lightly-staining belt, which we have termed the "intermediate zone." Outside of this, again, is a ring, forming the wall of the lesion, which stains intensely blue. This, too, is composed of tissue killed or damaged by the heat. It presents a ragged surface, where the coagulum has pulled away. To it we have applied the name "necrotic wall." These details are not shown in Figures 1 and 2. Beyond the necrotic wall, and rather sharply delimited from it, is a "peripheral zone" of pale blue (well seen in Fig. 1), which gradually fades out into the surrounding normal brain tissue. It varies somewhat in extent in the different brains, at the same stage, and is present only in early stages.

Hence the upper end of the stab presents a series of concentric, approximately circular zones, differing in intensity of staining. The regions termed the coagulum, the intermediate zone and the necrotic wall correspond respectively to what Coen[7] has described as the zones of "necrosis," "fatty degeneration" and "inflammation."

Often numerous dark blue spots are seen with the binocular on the surface in the vicinity of the stab. These are pia-arachnoid cells which have taken the vital stain. It is evident, too, that the superficial blood vessels on the injured side, supplying or draining the traumatized area, stand out by reason of their marked blue color in sharp contrast to the corresponding ones on the opposite side, in which the stain is often scarcely perceptible. Normally, as is well known, blood vessels stain quite plainly and diffusely with trypan blue, but here the staining is much increased over normal. The dura, too, in the vicinity of the stab, shows a strong blue staining, and frequently vitally stained cells may be observed in it.

If such a stab is cut transversely into slices the deeper portions show the same features: a central dense blue coagulum, often containing blood clot in the needle track, surrounded by a blue necrotic wall, sharply delimited from the more peripheral pale blue zone. As on the surface, we find interposed between the coagulum and the necrotic wall a loose fragmented zone, frequently containing blood clot.

These transverse slabs, when cleared in oil of wintergreen, show the different zones very distinctly (Fig. 4, from the six-day stage). The staining in the central plug of coagulated tissue is found to be fairly homogeneous, but blue granules may be made out in it with the binocular during the first day or two, which represent diffusely stained dead cells. A little later vitally stained macrophages are found. Similar blue-stained cells in the necrotic wall are found in stages from the first to the sixth day or later. The masses of extravasated blood are rendered very conspicuous. Often one can see that the blue cells follow the lines of the blood vessels. These are vitally stained cells of the endothelium and of the adventitia; it may be, too, that they are ameboid phagocytes which have wandered to these vessels. They traverse regions pervaded by a diffuse blue coloration; in Figure 4 they may be seen to radiate from the stab region. In pieces from the cortex they give the effect of a forest of slender straight trees as they follow their direct courses perpendicular to the surface.

Thus a well defined color pattern is presented by the upper end of the stab, and by cross sections of it, the elements of the picture corresponding to the different parts of the lesion.

By splitting the lesion longitudinally, the above mentioned regions are revealed in their full extent (Fig. 3, twelve-hour stage). Such sections were usually made transversely to the long axis of the brain. The vitally stained traumatized area is even more conspicuous than when seen from the top, and the contrast with the rest of the brain is very marked. The entire injured region, bluish in staining, is in shape like a truncated cone (as Coen has described it), with its base at the brain surface and its apex corresponding with the region around the point of the needle at its position of maximum penetration. Occupying the center, appears the long narrow wedge of coagulum—ragged and dirty blue—tapering from the upper surface of the brain toward the base, through the cortex, corpus callosum, and often thalamus, lateral ventricle and choroid plexus. The interior of the coagulum, marking the path of the needle, contains extravasated blood, and this has oozed into many of the spaces of the coagulum and the surrounding loose intermediate zone. Outside of the latter region appears the densely blue necrotic wall of the stab, the upper end of which was seen on the surface as a blue ring. As on the surface, it is sharply delimited from the tissue around it by reason of its more intense staining. Medially

it presents a ragged surface. As before the binocular microscope discloses in it blue dots, which prove, on examination with the compound microscope, to be dead nerve cells, as well as vitally stained living macrophages. Peripherally there is a variable amount of diffuse pale staining, widest at the top, which, as on the surface, fades into the surroundings.

By clearing a thick slice from such a preparation the dye deposits are vividly brought out, as in Figure 5 (six-day stage). Figure 6 presents a small area from this field, greatly enlarged. Here we see many dead cells and some living, vitally stained macrophages. In the sections of this period there are not found nearly so many stained macrophages as such a slice of cleared tissue would lead us to expect. In the lesion itself there are hardly any. There is much diffuse blue, due to the collection of dye in the exudate. Lines of blue cells along the blood vessels are seen, like those in the cross sections.

These findings are best understood by an analysis of the factors concerned in the production of the injury. During the process of stabbing, the upper end of the lesion was subjected to greater heat than the lower end, for not only did a wider part of the conical needle come into contact with this area, but it was exposed to the entire length of the inserted portion of the needle, both while entering and leaving. The hottest part of the needle was applied here also, for as it penetrated it became progressively cooler. Hence it is evident that the upper portion was more severely burned than that lower down, so that the conical shape of the injured area is explained.

The effect of the heating is to sear a cylinder—or rather a cone—of tissue, immediately about the needle. This "coagulum" pulls away from the surrounding parts, into which steam is forced. Thus a looser area, which we have called the intermediate zone, is produced, and into it fluid exudate and blood penetrate. Around this intermediate zone the brain tissue is severely injured by the heat, and has been called the necrotic wall. Its vessels quickly become thrombosed, as was demonstrated in a cleared specimen the vessels of which were injected with Prussian blue. The central mass is thus temporarily deprived of blood supply. In the necrotic wall the damage, of course, is greatest next to the center, and outwardly diminishes gradually.

These injured parts soon become flooded with tissue fluid laden with the dye, and rapidly absorb it. Many authors (Goldmann,[6] MacCurdy and Evans[5] et al.) have shown that dead tissue takes up the dye and stains diffusely; indeed such behavior on the part of cells toward the dye has been looked on as an evidence of death. Thus it was to be expected that the injured area would be quite intensely blue, and when the relative densities of the different zones to which we have referred are considered it is quite in order that most of the staining

should be found in the necrotic wall, and in the coagulum. The material stained appears not to be fat, but the actual protoplasm of the damaged cells.

In addition to this diffuse staining of the dead tissue there is to be considered, during a limited period, as we shall see, a slight staining of the macrophages, most marked about the second and third days, which intensifies very slightly the coloration.

Staining Variations with Stage of Repair.—Having gained a definite conception of the macroscopic characters of a stained injured brain we are in a position to compare the different stages, in order to study the variations in coloration at the successive repair periods. A careful inspection of the upper ends of the lesions and split sections in the entire Series 27 shows that the staining of the injured tissue very rapidly reaches its maximum brilliancy. Fairly bright at the one-hour stage, and quite well marked at two and one-half hours, it appears at the sixth hour almost as strong as at any later time. All the zones are very clear cut at this stage. The stain remains practically unimpaired until the end of the third day, following which it gradually fades, and by the tenth day is quite weak. After this stage it is practically negligible, although faint traces were noted as late as the thirty-fifth day; several earlier specimens, however, did not show any staining, and none of the later ones did. The period during which the necrotized tissue stains with trypan blue, then, extends from the first hour, or even before, to about the tenth day.

This survey reveals a very rapid diffusion of the dye into the necrotic tissue, for in six hours the staining has practically reached its maximum, as far as can be ascertained from inspection. The subsequent lessening of staining intensity may be laid to the gradual absorption of stainable material. In support of this we note that the sections show a progressive rarefaction of the injured tissue. Perhaps a less important factor in this diminution in staining power is to be found in the changes occurring in the dead tissue, which prevent its taking up the dye. The finding of unabsorbed remnants of injured tissue as late as the sixty-second day — long after any diffuse blue staining is visible—favors the latter view. It is not improbable that the composition of the necrotized tissue is gradually changed, through loss of the more soluble albuminous materials, leaving the more stable elements, which do not take up the dye readily. On the whole, however, the use of the vital dye affords a graphic and reliable picture of the process of resorption of the moribund tissue.

If the concentration of dye is increased, the staining, as would be expected, is more dense. Thus in a special case at the two and one-half hour stage, where a solution of dye was used in strength greater than

1 per cent., the staining was more dense than in the other members of the same stage. The amount of stained tissue, of course, varies directly with the severity of the injury. However, even where the operative and staining technic was uniform, differences in the intensity of staining of the lesions in different animals were sometimes noted, these being directly related to the general staining of the animal. When the body tissues as a whole are lightly stained the injured parts are also. Allowance was made for this in making generalizations.

It is interesting to study this staining as it occurs in the different zones of the lesion. In the coagulum the color was quite well marked in the one-hour stage; with further exposure to the dye the color became rapidly intensified up to the twelfth hour, remaining uniformly bright until the third day, and then diminishing progressively until the tenth day. Though traces were present up to the twenty-fourth day, they were exceedingly slight; indeed the coagulum can scarcely be said to be stained after the tenth day. Thus the staining of the coagulum, in respect to its onset, duration and disappearance, follows the scheme of the staining of the entire lesion, and the same interpretation may be accorded it.

The staining of the necrotic wall is quite comparable to that of the coagulum; it is a little more marked in the early stages—probably because of easier access to the dye through intact blood vessels. Then, too, the vital staining of the macrophages on the second and third day, which will be referred to later, is a source of some slight accession of color in the necrotic wall at this time. At many later stages, such as that of the third day, after the dye has had time to diffuse into it, the coagulum has stained more intensely than the necrotic wall. There is probably then less stainable material in the necrotic wall, for here, no doubt, absorption commences sooner, due to better vascular organization. In the necrotic wall, too, the granules due to dead nerve cells are usually more distinct, as cleared specimens show, than in the coagulum, since in the latter the individual cells are, as a rule, destroyed beyond recognition.

The staining in the "peripheral area" is much paler than that in the coagulum and necrotic wall; indeed the contrast is quite striking (Figs. 1, 2 and 3). Here there are fewer dead cells, although these are fairly numerous, especially in the border zone between this region and the necrotic wall. This border zone, as will appear later, marks the limit between the tissue which will remain and that which will be absorbed. Sometimes this pale staining involves the opposite cerebral hemisphere, an area adjoining the stained region of the injured side appearing blue, as in the two and one-half-hour (S27-35), six-hour (S27-24), and two-day (S27-8) stages.

This staining develops almost coincidently with the staining of the necrotized tissue; but very little of it exists after the fourth day, and almost all, if not all, traces have disappeared by the tenth day. A graphic illustration of its disappearance is afforded by comparing Figure 1, of the twelfth hour, with Figure 2, of the sixth day.

It is difficult to explain this peculiar coloration. We may assume that it is due to some change in the tissue, which temporarily lowers its vitality, permitting the cells to take up a little dye; and that they subsequently recover from this injury, with the exception of the cells actually killed in the vicinity of the lesion. This change may be supposed to be in the nature of a shock, and a temporary disturbance of the equilibrium of the protoplasm of the cells, which disappears later. If this were true one would look for dye within the cells proper, and consequently a granular picture would present itself in the cleared preparation under the binocular microscope. This we do not find, except in dead cells in the region adjoining the necrotic wall. Then, too, the sections reveal in this zone only a very little intracellular dye. This is found in a few neuroglia cells, and is quite inadequate to account for the color.

It seems to us, therefore, that the most plausible explanation for this pale staining is that it is due to an edema of the tissue about the injury, consequent on the inflammatory reaction, and that the intercellular spaces are charged with the dye, rather than the cells. Fluid undoubtedly exudes from the blood vessels of such a region, and since this fluid is loaded with the dye, the latter becomes sufficiently concentrated to be easily visible.

It is noteworthy that the tissue in which the stain appears does not become completely absorbed, as the necrotized tissue does, but retains much of its character as nerve tissue, although in the neighborhood of the lesion many of the cells are killed and shrink, losing their normal appearance. Then, too, the tissue around the necrotic wall becomes more porous and open in texture than that of the normal brain tissue, and it is certain that it undergoes much change, as will be seen on reference to the sections. The presence in this area of trypanophilic neuroglia cells points to the presence of fluid exudate.

A similar pale staining was found in the brains of animals that had received a blow on the head (S28) thus, producing a concussion of the brain, or even a lesion due to a depressed fracture. In S28-1 (eighteen-hour stage, one injection of 4 c.c. dye for eighteen hours) the cortex underlying the area of impact showed a distinct, though very pale, diffuse staining. In S28-2 (four-day stage, one injection of 4 c.c. dye for twenty-four hours) the surface of almost the entire cerebral hemisphere was of a pale diffuse blue, more marked than in the eighteen-hour stage. It is associated with a staining of the pia-

arachnoid cells and the blood vessels. There was a distinct lesion of the brain in this case, due to the penetration into the cortex of a spicule of bone from a depressed fracture, and here we find the same dense staining of necrotized tissue that was noted in the coagulum and necrotic wall of S27. There were some slight hemorrhages over the cortex. In S28-3 (eleven-day stage, 8 c.c. of dye in two injections, forty-eight and twenty-four hours before killing) there was no staining.

In these cases it is probable that the mechanical effect of the shock caused an inflammatory edema, as in the hot-stab cases, and that the staining arose in the same way.

A similar pale diffuse staining was also noted in the brain and cord in rats that were the subjects of experimental meningitis. The cause was doubtless the toxins arising from the infection, for the staining was obvious for a considerable depth under the infected meninges.

We may refer briefly to the staining of the blood vessels surrounding the lesion, in S27 (seen on the top of the brains in Figures 1 and 2) as revealed by a comparison of the different stages of the series. This staining comes on rapidly; at the one-hour stage the vessels are quite markedly blue, and at two and one-half hours the coloration is as bright as at any subsequent stage. It remains brilliant until the fourth or fifth day, rapidly diminishes, and is not found after the tenth day. It involves the efferent and afferent vessels. In cases where the diffuse pale blue extends over to the opposite hemisphere (as in S27-24) the vessels of this side appear stained also, but not so brightly as on the injured side. The middle cerebral artery, being large and superficial, is usually the most brilliantly stained vessel. This vessel staining was noted in one depressed fracture case (S28-2), of the fourth day.

The staining of the vessels is thus synchronous with the general staining of the lesion, and it seems to be intimately linked with this, and with the inflammatory process. It is certain that in the vessels of the inflammatory region some change has taken place. This change may involve the permeability of the wall, permitting the passage of exudate into the area of inflammation or promoting absorption of the soluble exudate. Histologic examination disclosed nothing beyond a deepening of the usual diffuse blue staining of the wall.

We may here say a word as to the staining of the pia-arachnoid cells, as they are seen on the upper surface of the brain, in the neighborhood of the lesion, under the binocular microscope. They were not noted until the sixth hour. This may be because not enough dye was present in the cell before this to be visible, or that there is a latent period between the application of the stimulus and the onset of dye ingestion. It is noteworthy that the pia-arachnoid cells of the brain of the rat do not, under normal circumstances, stain. Stained pia-arachnoid cells in the neighborhood of the lesion were found in prac-

tically all cases from the sixth hour to the sixth day, and they were noted in many, though not in all, cases later than this, up to the twenty-fourth day. Occasionally they were quite remote from the lesions. In a depressed fracture case of the fourth day (S28-2) we found similar stained pia-arachnoid cells in the traumatized area.

These cells, like the phagocytes within the brain substances, are evidently part of the organization for getting rid of waste material in and around the injured area. They will be considered further in the study of the sections.

In stages ranging from the first hour to the sixth day the choroid plexus on the injured side was stained more intensely than that on the normal side. This is not surprising, in view of its proximity to the injury; frequently it shares in this. For the same reason, and also because of the stained macrophages it contains, the dura around the wound is darker blue than elsewhere.

The binocular microscope reveals a very interesting condition in the peripheral zone of many of the cleared slabs, which has already been referred to. Striking rows of cells are seen, which were found to trace out the course of vessels (Figures 4 and 6). These were very conspicuous in the cortex, as well as in the deeper brain substance, and were noted at stages of the first (S27-5), second (S27-7, S27-8), third (S27-37, S27-39), fourth (S27-9) and sixth (S27-14) days. Not only phagocytic endothelium, but perivascular cells as well, are thus brought out. More will be said as to this interesting condition in the description of the sections.

HISTOPATHOLOGY

In the study of the sections an account of a typical lesion will first be given, followed by a brief survey of the principal changes occurring as a result of the processes of inflammation and repair. The macrophages, which appeared in injuries of all kinds, as we expected, will then be described, especially with regard to their vital staining features.

Typical Lesion.—If from an animal of Series 27, killed shortly after the operation, before the inflammatory reaction has become evident, a brain section be so cut as to split the stab, the picture presented will recall that seen in the gross preparations. Figure 12, a low power from the six-hour stage, presents a typical appearance. In the lesion the various concentric zones already described are seen. The coagulum is somewhat homogeneous and glassy in appearance, and often more or less broken. In it are the remains of seared cells, fibers and extravasated blood. In places the microscope discloses areas which are finely reticular in structure. The dead cells and fragments thereof stain a dense blue.

In the intermediate zone the loose, open spaces contain serous exudate and blood, but there are relatively few cells in the early stages. In the necrotic wall, dead nerve and neuroglia cells are found, stained diffusely blue, and showing little or no cellular detail. The inner margin of this wall is irregular and, of course, presents the greatest amount of cell damage. Here the blood vessels are thrombosed and extravasated blood is abundant. Farther out the injury becomes progressively less, leading into the narrow transitional zone bordering the peripheral area. Here it is seen that the ganglion cells, being more delicate, are killed farther out in the nerve tissue than the neuroglia and vascular elements. This feature was very marked in the cortex and in the layers of the cornu ammonis. These dead cells dwindle away as we range out into the peripheral zone, which passes insensibly into the surrounding normal nerve tissue. These features, of course, vary somewhat with the severity of the injury. Thus when a small needle is used, or one relatively cool, the damage is less and the lesion smaller.

Survey of the Healing Process.—As we glance over the sections representing the successive stages of healing it is not long before we are able to recognize marked changes which are well demonstrated in the photomicrographs, Figures 12 to 21, from Series 27. With advance of inflammation and repair the early morphologic features of the lesion are gradually lost. The injured area rapidly becomes invaded by granulation tissue, coming from the surrounding blood vessels and from the pia-arachnoid. Young vascular sprouts, fibroblasts and a few polymorphonuclears soon appear, and a multitude of mononuclear phagocytes quickly takes possession of the entire area. The coagulum and necrotic wall, with the absorption of their substance, melt away, becoming more open, their spaces affording growth channels for fibroblasts, young vessels and phagocytes. The characteristic zoned pattern is thus speedily obliterated.

Soon a sheet of cells forms between the necrotized elements, destined for absorption, and the surrounding damaged, but not completely destroyed brain wall, which is to be conserved. It is represented at first by an aggregation of fibroblasts and other elements, among which are many mononuclear phagocytes. From this mass a definitive membrane is gradually condensed. By the sixth day its outlines are becoming visible, and it was well marked at the fifteen-day stage. It is directly continuous above with the pia-arachnoid (Figs. 15, 16, 18, etc.), and gives the impression of having grown down from this membrane. Fibroblasts from the surrounding blood vessels doubtless contribute to it, and it may be that the neuroglia reinforce it by building up a sclerotic zone around it, as Tschistowitsch[8] believes. Coen[7]

derives it from pia, perivascular and neuroglia elements. This membrane, which is sometimes thin and poorly marked, is simply the peripheral border of the core of loose fibrous tissue which comes to occupy the brain defect, and which eventually replaces most, if not all, of the necrotized tissue. The spaces in the scar, which are numerous, and apparently intercommunicating, seem to be continuous outwardly with the subarachnoid space, and are thus probably filled with cerebrospinal fluid. The blood vessels in it, which at first are abundant, affording a thoroughfare for waste product removal, gradually disappear. The mononuclear phagocytes, so numerous in the early stages, slowly decrease in number, but were found in the latest stage examined — that of seventy-four days.

The brain tissue outside of this membrane shows evidence of damage which varies inversely as the distance from the needle. In early stages the inflammatory process shows the usual vascular and cellular changes. Neuroglia and endothelial cells are awakened into phagocytic activity which, as will be seen, shows itself in the appearance of dye granules in these cells in the vitally stained animals. This is the region which has been referred to as manifesting a pale diffuse staining with trypan blue. After the inflammatory conflagration has swept through this zone there persists a residue of the original tissue in which the damage is greater or less according to the distance from the stab. We have already noted the presence of dead cells, especially near the needle track. These cells shrink, show degenerative changes histologically and, in the early stages, stain densely with trypan blue, including the nucleus. Their attenuated corpses may remain in situ for weeks and even months. The intercellular substance shows a porous and reticular condition (Figs. 24, 26); the meshes of this reticulum are largest next to the separating membrane, and gradually become finer peripherally, passing over into the normal nerve substance.

Some of these photomicrographs require special elucidation. Figure 14 reveals the characteristic appearance of the three-day stage, the coagulum and extravasated blood being plainly shown, with the conspicuous agglomeration of macrophages between the coagulum and the edges of the necrotic wall. Figure 15 (fifteen-day stage) shows a case where the injury was relatively slight, and healing correspondingly rapid. Hence most of the dead tissue has been absorbed, the defect being occupied by large open spaces, with a reticulum of scar tissue containing a little débris and some macrophages, the whole bounded by a well marked membrane. In Figure 16 (twenty-four-day stage) healing has not progressed so far, probably because the injury is more extensive than in the preceding stage, so that the edges of the wound are not so definitely outlined, less absorption has occurred, and the membrane is not so well developed, although it can be seen at the upper

part of the photograph lining the right side of the coagulum. Macrophages and fibroblasts which have grown into the coagulum at this stage of healing are pictured in Figure 17. When we turn to Figure 18 of the sixty-two-day stage we find that some shreds of tissue still remain, pointing to the fact that not all of the defunct brain substance is speedily absorbed. This is in harmony with the findings of Coen and others. The defect, however, is principally filled by a mass of very open reticulum, in which are caught blood cells and macrophages. The shrinking of this scar tissue, with a gradual inpushing of the surrounding brain walls, doubtless reduces the size of the lesion, but in no stage examined was the defect completely obliterated, and as late as the sixty-second day it was quite large. In the more severe injuries the defect probably is never filled. The membrane of pia-arachnoid cells is well formed, and has completely isolated the débris to be absorbed from the surrounding brain tissue. It is shown under high power in Figure 19. The end stage of the process is seen in Figure 20 of the seventy-four-day stage, where the membranes of the two sides of the wound are practically in apposition. This case, however, is from a slight injury, the wound having been made with a small needle.

A few stabs (fifth, seventh and eighth day stages) were cut transversely. These show the various zones most strikingly. The coagulum may be seen gradually breaking up, the fragments becoming enmeshed by the ingrowing granulation tissue. The lesion is filled, in early stages, with a dense plug of cells, which is quite sharply differentiated from the surrounding brain wall. The inner border of the peripheral zone appears as a distinct narrow strip of coarse reticulum, in which cells are very scarce.

Vitally Stained Granules in Coagulum.—The diffuse staining of the dead tissue has been described with the gross material, and it is much more satisfactorily studied there than in the sections. It is possible to make out a distinct staining of the coagulum and necrotic wall, even in thin sections, in the early stages, but in no case was the faint staining of the peripheral zone appreciable in the sections. There is, however, an interesting feature of the staining of the coagulum which should be described here. It consists in a multitude of small bright blue granules, in appearance quite like the "dye granules" found within the cytoplasm of macrophages, which occur among the débris of nerve cells, fibers and other material composing the coagulum (Fig. 27). These granules are usually small, round and scattered singly or in small clumps. They vary in size from those so small as to be seen with difficulty with the oil immersion to aggregations of dye measuring about one fifth of the diameter of a red blood cell. Such large granules, however, are rare, most of them being very small. They are

intensely stained, and stand out in sharp contrast to the rest of the coagulum, which shows the usual diffuse coloring of dead tissue. They do not occur in all parts of the coagulum, but only in certain loose areas, reticular in structure, and the appearance is as though the granules were caught in the meshes of this. They are not found in the necrotic wall nor in the outlying brain substance. They were first seen at the six-hour stage. Earlier than this the dye has apparently not had time to concentrate sufficiently to render them visible. In the one-day stage they are more numerous, and in the two-day stage the number is still greater. Traces were noted at the third day.

Thus we have occurring in dead tissue a phenomenon — that of the segregation of the molecules of the dyestuff, trypan blue, to form distinct granular masses, easily seen with the higher powers of the microscope — which we have heretofore been accustomed to associate with the activity of living protoplasm. These granules are probably minute stained masses of protoplasm, highly concentrated, due to the action of the heat, and of such character that they absorb the dye with great avidity, and are thus able to accumulate so much of it, by apparently purely physical means, that they appear very distinct.

The fact that they become progressively more and more numerous from the sixth hour to the second day suggests that the protoplasmic granules, which appear to form the basis of them, vary in their ability to attract the dye, so that the more avid granules are stained first. They occur in the special cases (later to be described) where the dye was given at the time of operation and the animal allowed to live on until the eleventh or fifteenth day; here absorption of the coagulum has evidently been delayed. The fact that they do not occur in Series 27 after the third day suggests that the basis of their formation, the granule of concentrated protoplasm, is speedily absorbed in the normal repair process, or is so changed that it no longer takes up the dye.

In the two-day stage we have the opportunity of comparing these granules with the intracellular granules of the living macrophages which have now invaded the coagulum, and the resemblance is striking indeed; it is quite probable that this would not be so close in fresh material. The granules are never scattered over open spaces in the coagulum, as would be the case if they were simply minute coagula precipitated from the plasma, but always appear in the solid, though tenuous, remains of the coagulum.

In their genesis they seem to be extreme cases of the same process which appears in the absorption of dye by any dead or inert protoplasm; they are thus distinct in this respect from the granule which occurs within the cytoplasm of the macrophage, which (according to current hypotheses) is formed by a phagocytosis of the dye and a

concentration of the same within definite areas of the cytoplasm. It is of interest to point out, however, that we have here a distinct type of dye granule formation which cannot be attributed to cellular activity. Up to this time dye granules have been intracellular, whether formed by the staining of preformed material, or by the so-called "vital activity" of the cell expressing itself in phagocytosis. These observations, although brief, serve to record the extracellular occurrence of trypan blue in granular form.

THE MACROPHAGES OF BRAIN WOUNDS

General Survey.—We come now to a consideration of the mononuclear phagocytes which play such an important rôle in the process of brain healing just described. A complete histologic examination of these cells is not intended, and is quite unnecessary, since the literature contains so much regarding them (e. g., the work of Alzheimer[9] and, more recently, of Essick[10]). In this article, therefore, we shall content ourselves with but a cursory notice of some of the more salient features of the cells, passing on rapidly to a discussion of their behavior toward trypan blue, in the experiments carried out. Their general characteristics were found to correspond to the abundant descriptions given by the many authors who have written on the subject, and who have referred to the cells by the term "Körnchenzellen," and by various other designations.

They were not conspicuous in the brain tissue until the second day after the injury, though it is probable that their precursors were on the field some time before their phagocytic activities were so pronounced as to lead to their detection. They increased very quickly, and by the third or fourth day their numbers had reached the maximum. Following this they diminished gradually until the last stage examined, that of seventy-four days, when they were very few. It is possible that they remain in the defect even longer than this. There is some variation in this general rule, as, for instance, fewer were found on the fifteenth day than on the twenty-fourth, but this is due, doubtless, as we have already mentioned, to the relative lightness of the injury in the former case.

As to their position in the lesion, at the time when the first cells were found, on the second day, they inhabited the loose zone around the necrotic plug, and also the necrotic wall. It would seem that they are ameboid, and have wandered into these regions from the sur-

9. Alzheimer, A.: Beiträge zur Kenntnis der pathologischen Neurologia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe, Histol. u. Histopathol. Arb. über die Grosshirnrinde (Nissl), Jena **3**:401, 1909.

10. Essick, C. R.: Pathology of Experimental Traumatic Abscess of the Brain, Arch. Neurol. & Psychiat. **1**:673, 1919.

rounding tissue. They are to be found in the neighboring brain substance also at this stage, scattered among the cells and fibers (Figs. 13 and 24). As the coagulum softened they gradually invaded it, as seen on the tenth day; indeed quite a number were found in it on the third day. Sometimes the macrophages occurred in closely packed masses — the "Körnchenkugeln" of Gluge[11] — giving the impression of a syncytium. As the limiting membrane which we have described forms, most of the phagocytes are found in the space which it encloses, and after it has become well marked there are few or no phagocytes to be found in the outlying brain tissue. Often the phagocytes are in the membrane itself. With the disappearance of the débris the macrophages decrease in number and are found in the meshes of the scar tissue, occupying the defect.

The relation of the macrophages to the blood vessels traversing the blue-clouded zone of inflammation is worthy of note, and has been referred to. Hypertrophied endothelial cells, so well known to pathologists, were often seen in the early stages, as at the third day. Frequently macrophages were found in the adventia and perivascular spaces. Often they occurred closely applied to the outside of the vessel wall, and even extended along it. This relationship, in the vitally stained specimen, led to the vessels being outlined by blue cells, so strikingly seen in the cleared slabs. When the capillaries invade the coagulum these cells can be seen composing their walls or closely applied to them, as well as lying free in the perivascular spaces and beyond. This important relation will be discussed at greater length with the fresh tissue.

The average size of the macrophages at the different stages of brain repair was determined by selecting ten representative cells in a section from each of the fifteen most representative specimens, extending throughout S27, and making careful measurements of the longest diameter by the aid of the camera lucida; an average was then taken. This method was fairly accurate, since the shape of the cells examined was approximately the same. No very wide variation in size due to the stage of repair was noted. When the cells are proliferating rapidly, as at the third day, the average size is somewhat smaller (11.42 microns). As mitosis becomes less frequent in the succeeding stages the size increases up to 17.9 microns at the fifteenth-day stage, and then decreases gradually to 13 microns by the thirty-fourth day, and to 10.6 microns by the seventy-fourth day stage. This gradual increase in size up to about the fifteenth-day period is due not only to the fact that the cells cease dividing, but also to the enormous amount of fat which they ingest, and which increases the volume of the cell.

11. Gluge, G.: Experimente über Encephalitis, Abhandlung z. Physiol. u. Path., No. 2, Jena, 1841, p. 13. (*vide* Essick 10.)

There was, of course, quite a difference in size in the cells of any one specimen, as, for instance, on the fifteenth day of repair, when cells were found to range between 10 microns and 42.7 microns (Fig. 10 shows a large cell), but this was an extreme case. The smallest cells, 7 microns, were noted on the second and tenth days, and the largest, 42.7 microns, on the fifteenth. A number of large cells were also found on the twenty-fourth day. The largest macrophages congregate in the region of the necrotic plug, and later occupy the space from which it has been removed. This is especially noticeable in the stages later than the fifteenth day.

By combining and averaging the size at the different stages it was found that the average long diameter of the macrophage, for the entire period from the second to the seventy-fourth day, inclusive, was 13.6 microns.

The shape of the macrophages, in the early stages, is very irregular. When found in crowded clumps they are polyhedral in form, and stellate outlines predominate in the looser groups. When lying free they are characteristically spherical or oval (Figs. 8 and 9). Rounded forms are the rule in the later stages (Fig. 17). Since they are ameboid it is probable that, especially in the earlier stages, they undergo frequent changes of form.

The cytoplasm is very voluminous in comparison with the nucleus. It varies in structure, of course, with the stage. It possesses the special property of being able to increase in size and to gather into itself materials from without which are stored within minute vacuoles. This evolution of the cytoplasm is quite rapid, so that the cells are of large size by the second day. This property gives to the cytoplasm a reticular appearance, especially in the sections prepared in the usual way, where the fat is dissolved out by the reagents. This reticulum becomes even more conspicuous with time, and so we find on the fifteenth day (Fig. 10), and later, typical examples of what have been termed "foam cells," the protoplasm being reduced to mere attenuated threads enmeshing the huge fat globules and aggregations of other foreign substances.

The material engulfed consists principally of dissolved protein and lipoids. The latter are particularly abundant in the brain, due to the large amount of myelin destroyed. Vacuoles, which probably represent fat, were found in all stages, including the seventy-fourth day. This substance was easily detected by the use of osmic acid, and by other methods. As early as the third day the cells contain as much fat for their size as they do in any later stage, although, of course, the cells are larger, as we have seen, in the later stages. The amount that each cell contains remains at this high level for two weeks or longer. The globules are of varying size, some being half the diameter of the cell,

while others are very small. There is not much difference in their size from stage to stage, but, if anything, in the earlier stages the larger globules are proportionally a little more numerous. We will say more as to fat with the description of the fresh material. The osmic acid preparations show plainly the zones where fat-laden cells are most thickly congregated. Thus in S27-49 (three-day stage), transverse sections of the stab show a heavy ring of black cells (representing a special concentration of macrophages loaded with fat) just outside of the necrotic wall. This is especially clear cut in the transparent preparations. This ring of cells is not demonstrated with trypan blue.

Among the most conspicuous of the intracellular foreign materials is the blood pigment, which was found from the third to the seventy-fourth days, inclusive. It is easily recognized by the golden yellow appearance of the granule in the cytoplasm, and by appropriate methods of staining for iron. It is most abundant about the fifteenth day (Fig. 11). In the earlier stages (as at the sixth day) a few ingested red cells were found. It is an interesting point that there may be found closely associated in the same area of extravasated blood, macrophages whose cytoplasm is filled with golden yellow pigment, and others which do not contain a trace of this, these cells being otherwise apparently identical. Thus some of the cells appear to be especially developed for certain functions.

The blood pigment within the macrophage shows the familiar difference in tinctorial reaction with eosin, as compared with free red cells, pointing to a change having taken place in the hemoglobin, probably due to the activity of the phagocyte. Aggregations of extravasated red cells were frequently noted in the lesions, and were found as late as the thirty-fourth day of repair. The absorption of red cells in these aseptic injuries in rat brains seems to be slower than that of the red cells in the vicinity of abscesses in the brains of cats described by Essick.[10] It may be that here the infection hastened in some way the absorption of the red corpuscles.

In addition to materials apparently in a liquid form, the usual cell fragments, and even whole cells, were found engulfed by the macrophages. On the whole, it may be said that in the earlier stages, as from the second to the twelfth or fifteenth day, fat was the most conspicuous cell content, whereas later hemoglobin residue became more and more the dominant enclosure.

The nucleus of the macrophage is rounded or oval in form, and is situated characteristically eccentrically. It is well supplied with chromatin, and has usually a large nucleolus. As a rule, it is single, but not infrequently cells with two nuclei are found, suggesting an

amitotic nuclear division (Macklin[12]). There was no constant variation in size of the nucleus with that of the cell as a whole; there was, too, no constant change in the chromatin material with advance in the repair process, nor did the size of the nucleus vary with the stage of repair. The average long diameter of the nucleus, as taken from stages of the second, twenty-fourth and sixty-second days, was 5.1 microns.

The method of multiplication of the macrophages is quite evidently by mitosis. Many dividing figures were found on the second day, and they were particularly abundant on the third day. They were found as late as the sixth day. No evidences of direct cell division were found. The presence of dye, fat, and other inclusions within the cytoplasm does not prevent division (as other workers have noted in similar cases), for we found many dividing cells which presented this condition.

In these aseptic cases but few polymorphonuclear leukocytes were found associated with the macrophages, as in the fracture cases (Macklin[2]) and, like these latter, they contained no dye granules.

Vital Staining of Macrophages.—The most interesting feature of the macrophages in connection with this investigation is their behavior toward trypan blue. The staining is notable for its short duration and for its weakness. The first macrophages which were found to contain dye granules were those of the pia-arachnoid in the vicinity of the lesion. In the sections these were first noted at the end of twenty-four hours, although some of the earlier stages examined with the binocular microscope disclosed them. They will be described in a special section to be devoted to the pia-arachnoid phagocytes.

In the macrophages of the brain lesion dye granules were first seen in the cells at the end of forty-eight hours. Apparently, as the cells develop phagocytic properties they take up the dye from the surrounding fluids. At this period the ingested dye was slight in amount, and it was necessary to search carefully in order to find it, although it was more conspicuous at this stage, and shortly after, than at any other. The coloration was best studied in thin sections cleared without counterstaining. At this stage many cells of identical morphologic type to those vitally stained were observed to contain no dye, and many also which had but very little. Indeed, the actual proportion of cells in which dye could be demonstrated, as compared with the unstained cells, was small. Cells with and without dye inclusions, but all evidently macrophages, were often mixed indiscriminately together in close association. Similarly, it will be recalled, we found macrophages

12. Macklin, C. C.: Amitosis in Cells Growing in Vitro, Biol. Bull. **30**: 445, 1916.

filled with blood pigment in close association with those containing none of it. Most of the vitally stained cells were present in the necrotic wall and intermediate zone, as we should expect, since most of the phagocytes are found here. In none of the cells was the dye content large in relation to the total volume of the cytoplasm (Fig. 8), and most of the space is taken up, even at this early stage, by fat. The dye and fat seem to occupy different parts of the cytoplasm, the dye granules lying in the interstices between the fat globules. Mitotic figures were numerous in these cells.

It is worthy of note that we find, farther out, in what we have termed the peripheral zone (even where the nerve tissue shows only slight damage) cells containing dye granules (Fig. 24). These are not associated with vessel walls or perivascular spaces, and are undoubtedly neuroglia cells. Except for their dye content they cannot be distinguished from the neuroglia cells farther out in the brain substance. It was impossible to stain them so as to demonstrate their specific tinctorial reactions as neuroglia, and at the same time preserve their dye granules, since the small amount of blue dye contained in them is totally obscured by neuroglia stains. It was easy, however, to study the general morphology and at the same time inspect the dye content in sections lightly washed with carmin. Hematoxylin and eosin preparations were, of course, used for comparison.

As one progressed nearer and nearer to the site of injury, more and more of these cells could be found, larger as they were encountered closer to the necrotic wall, until they finally occurred as free rounded or oval cells, lying in the intermediate zone. Their stimulation into phagocytic activity is probably due to their being situated in an area of inflammation. The amount of dye within these cells is so slight as to be quite insufficient of itself to account for even the meager amount of color that we find in the peripheral zone, in the gross specimens. This pale diffuse color, it will be remembered, is quite imperceptible in the sections, and is most apparent in the freshly fixed gross material.

This vital staining reaction on the part of the neuroglia cells, and the occurrence of a series of transitional forms leading from the neuroglia of the peripheral zone to the typical brain macrophages of the necrotized tissue, lead us to look on these cells as one source of the macrophages of the brain.

On the third day the vital staining of the macrophages is about the same as on the second (Fig. 9). It is probable that a little more dyestuff has been phagocytized, but, also, more of the débris has been taken up, so that the dye content is not increased relative to the total volume of the cytoplasm. There are at this stage also many phagocytes, filled with fat and blood pigment, which contain no dye; indeed

most of the cells do not contain it. Large numbers of mitotic figures appear here also, and some of the dividing cells enclose dye within their cytoplasm.

On the fourth day there is but little dye to be found in the cells and, in comparison to the amount of other material phagocytized, it is insignificant. It grows gradually less, and by the sixth day it is almost impossible to find in these free phagocytes any intracellular dye. Even when found the granules are small and few. After this no vitally staining phagocytes were found in S27 except a very few in the limiting membrane and its continuations, and in the brain tissue immediately surrounding the lesion. Scattered cells in these parts were found on the seventh and eighth days of repair. They were often in the perivascular sheaths. While plainly stained they were never conspicuous on account of their dye content. In form they were typically elongated and showed processes.

Briefly, then, we may say that in the lesion itself cells containing appreciable quantities of dye were found in the hot stab cases on the second and third days of repair, while on the fourth day the amount was very slight and on the sixth day it was hardly demonstrable.

Under the conditions of our experiments, then, it is obvious that the reaction of the macrophages toward the vital dye differs widely with the stage of repair. With advance in age and stage of development they fill up more and more with ingested material from the injured area, and their phagocytic powers become gradually fatigued. Hence it was to be expected that great variation in the results obtained would occur when we exposed cells to a standard treatment with the dye the cytoplasm of which was already occupied by varying amounts of foreign material. In stages later than forty-eight hours the fat and other débris have been in contact with the phagocytes longer than the dye has, and this discrepancy becomes more and more magnified with the passing of time. A cell of the fifth day, for instance, cannot be expected to give the same reaction toward the dye as one of the second day, for the latter is much younger, and has been exposed to the dye for the entire period of its hyperactivity owing to the stimulation of the trauma, whereas the five-day cell has been at work three days before the dye was exhibited to it, and by this time it has become filled with other material. It is not unlikely that it has become especially sensitive to the fat and protein débris which it encounters in its environment, and has become correspondingly insensitive toward other materials; and hence the dye finds it unresponsive. Indeed, the older the cell grows the less is it likely to take up the dye.

The same conditions obtain with phagocytes in tissue other than brain, for here, too, the staining power of the phagocytes gradually

diminishes, as Macklin[2] and others have shown. In these tissues, however, since fat is not so abundant, it does not so markedly preponderate over the dye in the cell's cystoplasm.

It would appear that, even after the macrophages, under the conditions of our experiments, failed to take up the dye from the fluids of their environment, they were still capable of phagocytosis, for we note a gradual increase of blood pigment within the phagocytes for some time after the sixth day. There is also reason for thinking that the cells are still taking up fat after the sixth day, for free fat is encountered in the lesion for some time after that (as is easily demonstrated by the use of osmic acid), and some of the cells gained appreciably in size. Moreover, the occurrence of diffusely stained débris up to the tenth day, or even later, shows that there is work then for the phagocytes. It may be that if the dye had been given in more massive doses, or had been exhibited over a longer period, that these cells could have been made to take it up. We did not expose these older cells to a treatment with the dye for a period longer than forty-eight hours. We did, however, expose cells, in several cases, from their beginning, to a prolonged treatment with the dye, as the following account will show.

Effect of Prolonged Staining.—The dye was administered at the time of operation (the usual hot stab) and twenty-four hours later, in the usual doses (15 c.c. in S27-47), but instead of killing the animals at the end of the forty-eight-hour staining period, as in the other series, we allowed them to live for varying lengths of time, so that the macrophages were exposed to the dye from their beginning to the time the animal was sacrificed. There was quite a high mortality, and the prolonged action of the dye was markedly toxic. Two cases survived long enough for use—one to the eleventh (S27-45) and one to the fifteenth day (S27-47).

The animal killed fifteen days after the operation, which thus had endured fifteen days of staining, showed all of its tissues much more distinctly colored than those of any other case. The presence of dye in the tissues points to the occurrence of some, at least, in the circulation, up to the time of death, for the experience of other workers has shown that in stained animals, which are allowed to survive, the dye diffuses out of the tissues until they are decolorized.

There was a diffuse bluish stain over the entire cortex, and the wound area was intensely blue, in contrast to that of fifteen days in Series 27. The coagulum was almost all present, whereas it should be largely resolved at this stage. It was stained at least as intensely as it was in any stage in Series 27. In it there were still myriads of the same dense blue granules which were described only for the early

stages of S27. These facts all point to an inhibition of the absorptive processes due to the toxic action of the dye. This may be exercised on the enzymes which liquefy the débris, or on the phagocytes which play such an important part in absorption.

When we examine the slides we find that the lesion is filled with very large macrophages. They were at least as numerous as in any case we had, and stained very markedly with the dye, in contrast to the cells of the corresponding stage of S27, which contained no dye. Not only is there very much more dye within the cells than in any of the cases of S27, but the cells are practically all stained. The dye is distributed throughout the cytoplasm, between the abundant fat and blood pigment inclusions, which are present. The cells are plainly alive, for the nuclei are unstained and they are quite evidently discharging their phagocytic functions; however, the slow absorption of the débris in these cases points, perhaps, to a slackness in activity of the phagocytes, due to intoxication by the dyestuff, so that there is some weight in the contention that these phagocytes are physiologically subnormal. In no case was the volume of the dye within the cell such as to lend any support to the argument that the cells failed to take up débris because all their potential space was occupied by dyestuff.

The only evidence of progress in healing which this case shows over the earlier stages of S27 is that the membrane has started to grow down from the pia-arachnoid to line the edges of the wound. It is of interest that many of the cells constituting this membrane are filled with blue granules. They do not resemble the fibroblasts about them, which contain no dye, and are probably to be looked on as ameboid arachnoid cells.

Comparison of Brain Macrophages with Those in Other Inflamed Tissues.—One of the outstanding features of the macrophages of the lesions in S27 is the marked difference in response to the vital dye, trypan blue, which they show as compared with the macrophages of other injured tissues. If we contrast the phagocytes from aseptic inflammatory areas of liver, spleen and lymph gland, which Tschaschin[1] found, and shows in his figures, or those from the damaged tissue around fractured bones, which Macklin[2] describes, we are struck with the enormous difference in their vital staining in comparison with the brain macrophages. In Macklin's fracture cases the animals were subjected to approximately the same treatment with the vital dye as were these brain-wound cases of S27. At the three-day stage, and even before, in the fracture series, Macklin found the area about the injured bone quite blue with these cells, which he terms "extraosseous" macrophages (in contrast to the "intraosseous" macrophages which later inhabit the spaces of the resolving callus). His slides (Fig. 7) show

enormous numbers of them, many being literally stuffed with the dye, whereas the cells from the brain wound cases of the same period contain but little dye by comparison. This difference is strikingly brought out by comparing slides, cleared without counterstaining, of brain wounds and fractured areas, of the three-day stage. In the latter the field appears very distinctly blue, whereas in the former the coloration is very weak indeed. The contrast is even more obvious in the slightly later stages; compare, for instance, the six-day stage of the fracture cases with that of the brain cases. In the latter, as we have seen, the dye content of the cells is practically nothing, whereas in the fracture cases (except in the young scar) there is usually an enormous amount of the dye within the cells. Then, too, stained cells in the fracture cases are found later than in the brain specimens.

Indeed so little dye is taken up by these brain phagocytes in contrast to the mononuclear phagocytes present in aseptic inflammation in other tissues as to call urgently for explanation. We can hardly suppose that the dye was any more accessible to the phagocytes of the fracture cases than to those of the brain cases, for in the brain there was much dye within the dead tissue, and thus there must have been an abundance of it available for the phagocytes of the vicinity. The soaking up of the dye by this dead tissue could not be looked on as depriving the phagocytic cells of their quota, for the entire amount of dye taken up by the dead tissue must have been insignificant as compared with the total amount of available dye in the circulation.

The assumption of an earlier or greater fatigue on the part of the brain cells, as contrasted with those of other inflammatory areas, to account for the greater amount of dye in the latter cells, has no basis of support, since in both cases the cells seem to be stimulated to the height of their phagocytic activities, and there is no reason for assuming that they would tire earlier in one case than in the other. It is possible that there is a greater volumetric proportion of débris to dye in the brain cases than in the lesions of other tissues, but this is difficult to prove. The fact that the cell goes on ingesting other materials after the sixth day (which is practically the last appearance of the dye), proves that the failure to take up more dye after the sixth day is not due to lack of potential cytoplasmic space. Nor does the attempted explanation based on difference in origin of the cells help us, it being claimed that the ectodermal neuroglia cells of the brain lesions do not show the same type of phagocytic activity as the phagocytes of other tissues, in that these neurogliogenous phagocytes are more specialized to ingest fat. It is difficult to prove this assumption, and, too, we do not know how large a proportion of the phagocytes come from the neuroglia cells; moreover, we do know that many of

the brain phagocytes come from cells of mesodermal origin, such as the endothelial cells, so that this explanation cannot be looked on as of importance.

We might assume that the dye granule is produced by some sort of union—physical or chemical—between the aggregations of material already in the cell and the dye, and to argue from this that the cell which contains the greatest amount of such material will appear most strongly stained. Further, we might say, that the reason we get more staining in the case of the macrophages of the fractures is because these cells have more material (probably of protein origin) within them which takes up the dye than have the cells of the brain tissue, which are largely filled with fat, a substance in which the dye does not dissolve, and with which it does not combine. However, Evans and Schulemann[13] and others are opposed to the view that the dye granule is produced by a staining of material preexisting in the cell, and find that the granules of the macrophage arise by concentration of the ultramicrons of the dye within minute vacuoles. Although Shipley[4] believes that the dye and other materials may become mixed together within the vacuole, he feels that this is to be looked on simply as a mechanical mixture, and he holds that the substances within the vacuole have been impounded there probably by virtue of the peculiar mechanism of the cell, working, it appears, through an adsorption of the various molecules on the vacuole wall as a preliminary to their penetration into its interior. Foreign material already within the cell vacuole may be presumed to be inert so far as exerting any attraction for the dye, or as acting to incarcerate it in any way, is concerned. Even assuming that the granules in the early stages were engendered by the concentration of dye in preexisting intracellular ingesta, it is difficult to explain why this material should so suddenly diminish in amount after the second and third days, while such substances as fat and blood pigment continue to be taken in.

Perhaps the most plausible explanation depends on the important chemical differences which these tissues show, in that there is much more fat in the brain (due to myelin breakdown) than in the fractured bone, and it may be that the phagocytes of the brain become specially developed to ingest this fat, whereas those of the fractured bone cases become specialized to ingest protein. However, this difference is only relative, for we must assume that there is a considerable amount of broken-down protein in the brain tissues, and also a goodly amount of fat in the fracture cases. Indeed in the fracture cases, notably about

13. Evans, H. M., and Schulemann, Werner: Ueber Natur und Genese der durch saure Farbstoffe entstehenden Vitalfärbungsgranula, Fol. Haematol. **19**:207, 1914.

the sixth day, cells with heavy loads of lipoid and but little dye were fairly frequent. On the whole, however, it is incontestable that there is more protein breakdown in the fracture cases, especially where muscle is damaged, and, vice versa, more free fat in the brain cases. We may assume, then, that the macrophages of brain tissue become especially developed to take up fat, because of the relatively enormous amount of it to which the cells are exposed, whereas, for the same reason, a similar preponderance of the products of proteolysis in the case of the fractures determines the larger amount of these materials which the cells take up. Finally, it must be assumed that the dye is more like the dissolved protein physically than it is like fat, and that hence the cells which are specialized to take up protein products ingest dye more readily than do those which are developed to take up fat.

These brain macrophages, too, are distinctive in that there were probably more cells without dye, even in the second and third day stages of S27, than with it, the converse being true of the fracture cases. This paucity of stained cells cannot be due to any inherent inability on the part of certain of the cells to take up dye, for in the prolonged staining cases, where the cells were given dye for an extended period from their beginning, they practically all stained. Thus the unstained cells are not essentially different from the stained. Fragmented forms, like those found in scarring areas in the fracture cases, were not noted.

There is still another important difference which presents itself when we compare these brain phagocytes with those found in wounds of other tissues. Tschaschin[1] found in his aseptic inflammatory tissue of spleen, lymph gland and liver a host of transitional cells, ranging from a small cell, looking like a lymphocyte, to the large "polyblast," or macrophage, and Maximow had previously noted the same condition. In Macklin's fracture cases an identical transition is very evident. Indeed it would seem probable that a great number of these macrophages are developed from small lymphocytoid cells, coming, apparently, largely from the blood stream. When we examine the brain cases, however, we find hardly a trace of such transitional cells, and it may be said with confidence that, if lymphocytoid cells contribute at all to the macrophages here, they do so in such small numbers as to be negligible.

In attempting to account for this condition it may be assumed that in the case of wounded brain there is not the same peremptory call for assistance from premacrophages from outlying regions that there is in the case of wounded muscle, liver, spleen, etc. This call, probably, is due to the diffusion into the blood stream of small quantities of split proteins.

Not only were there enormous numbers of transitional cells among the extraosseous macrophages of the fracture cases, but there were few mitoses, whereas in the brain cases there were very many mitoses. This points to a derivation of the cells of the peri-osseous tissue from a source outside the lesion, in contrast to the brain wounds, where the cells seemed to be derived from the brain tissue itself.

Tissue Transplants.—We thought that, by inserting into the brain wounds small quantities of other tissues it might perhaps be possible to attract thither premacrophages, and that these might even develop into macrophages of a more trypanophilic type, so bringing about a picture similar to that in aseptic inflammation of other parts. Accordingly, we planned, and carried out, several additional experiments. In three cases (Series 29) we inserted a piece of temporal muscle into a hole in the brain made by cutting, without burning, and examined at the second-day, sixth-day and tenth-day stages. Resolving muscle tissue, it was found in the fracture cases, was especially noteworthy because of the occurrence in it of enormous numbers of phagocytes loaded with dye, and also of myriads of transitional cells. In two cases (S30) we inserted similar pieces of temporal muscle into a hole burnt with a hot needle, as in S27. In S32 the hole in the brain made by cutting was filled with liver; two cases were prepared, and examined at the second-day and sixth-day stages. In two cases of S33 similar wounds were filled with spleen tissue and both examined on the second day. In all of these cases the tissues were sterile and fresh, and were taken from similar rats, killed at the time of operation.

In none of these cases were there found in the brain lesion any transitional cells, nor was there any increase in the number of macrophages. It cannot be denied that products from the breakdown of these tissues diffused into the surrounding fluids, but there is no evidence that they attracted phagocytes from the blood stream. There was some delay in healing, in these cases, due to the greater amount of tissue to be absorbed. The phagocytes of the surrounding brain did not develop any greater avidity for the dyestuff, and continued to show the meager staining which characterized the cells of S27. In size (by actual measurement), the phagocytes of these special cases did not show any material deviation from that of the cells of S27 Their position in the lesion was also similar, and they did not show any more mitotic figures. These experiments were, therefore, negative in giving us any explanation of the differences in staining intensity of the cells under discussion, or in enlightening us as to the origin of the brain phagocytes.

Abscess in Lesion.—In contrast to the negative results obtained in the foregoing experiments, were the observations made on a small abscess which occurred by accident in one of the cases operated on

as in Series 27, and which thus had to be omitted from the aseptic cases. It gave most interesting information as to the reaction of the macrophages toward the dye, under such conditions. The animal (S27-41) was killed at the twelfth day of repair.

In the gross the specimen was characterized by the dense blue color of the lesion (in contrast to the regular members of S27 of this stage, where the dye had almost, if not absolutely, faded), showing that the removal of débris has been somewhat delayed. The upper surface of the brain presented a dark blue plug, filling the defect, surrounded by a narrow, paler zone. In the hemisection this mass appeared particularly densely stained and projected above the brain contour, occupying the upper end of the defect like a cork in a bottle. This was the abscess. Lower down the blue staining extended almost to the end of the stab. There was practically no blue in the walls of the defect.

Sections through the stab (Fig. 22) show the small abscess occupying the aforementioned projecting plug. It consists of an aggregation of pus cells, enclosed by a well marked capsule of macrophages, which stain densely blue, and give to this tissue its deep color. Outside of this macrophagic wall is a fibrous zone, representing the membrane, described as effecting the delimitation of the field. This fibrous tissue is directly continuous above with the pia-arachnoid, which here is much thickened. Surrounding this membrane is the brain tissue.

Thick, clear and uncounterstained sections present a striking picture (Fig. 7). The macrophage zone stands out as a dense blue ring, the stain of which can be accounted for by the granules in these phagocytes. Within it the aggregation of polymorphonuclears is stained a pale diffuse blue, but no dye granules are demonstrable in these cells. Here and there among the polymorphonuclears, especially in the periphery of the collection, are macrophages which have wandered in. There are, of course, polymorphonuclears to be found in the macrophagic zone, but these become outwardly less and less in number. No dye granules were found in them. No bacteria were demonstrated, and the septic process appeared to be very subacute as compared with that obtaining in the experimental abscesses in cat brains described by Essick.[10]

These abscess-wall macrophages are large, and, when their contour can be discerned, they are more oval and elongated than those of the brain. From their close relation to the pia-arachnoid they seem to be developed from it.

An area from the section from which Figure 22 was photographed is seen in Figure 25. This shows the various layers of the abscess, the aggregation of pus cells in the center, the surrounding macrophage capsule, the enveloping fibrous tissue, and finally, sharply marked off

from it in places, the brain tissue. The latter shows, as in the aseptic cases, a much changed structure in the zone bordering the membrane, with loss of ganglion cells and a large meshed intercellular reticulum. A small group of dye containing macrophages, taken from this field, is shown at a higher magnification in Figure 23. It is easily possible to find macrophages here which do not contain dye, yet the majority do so. In Figure 23 the cytoplasm is shown of an indefinite contour, and, indeed, the impression is given of a syncytium.

Lower down in the stab the débris is being absorbed, as in S27, but somewhat more slowly, due to the superposed infection. The usual numbers of large, fat-laden macrophages are seen. They contain no dye, as in all the S27 cases after the sixth day, and thus stand in sharp contrast to the macrophages of the abscess wall. Indeed, the latter contain much more dye than did any of the brain macrophages, even in their most marked stages. This is strikingly shown when this specimen is compared with cleared slides from the second and third day stages of S27. The macrophages of the abscess wall, indeed, resemble, in their avidity for the vital dye, much more closely those found in the fracture cases. Their specialization to ingest the toxic products which have diffused out from the abscess has doubtless fitted them for the ingestion of the vital dye, and in this respect they are physiologically more like the macrophages of inflamed nonnervous tissue than they are like the macrophages of the brain lesions.

The difference which the macrophages of the abscess wall show, as compared with the neighboring polymorphonuclear leukocytes, in respect to their behavior toward the vital dye, is most striking, and speaks strongly in favor of the physiologic distinctness of these two cell types. The amount of dye contained in the mass of leukocytes is so slight as to be hardly observable, even in very thick sections cleared without counterstaining; indeed, at first glance at such a section it appears as though the contents had fallen out of the abscess cavity, and that we were seeing only the bright blue wall. The leukocytes of the abscess wall, and beyond it, show the same condition. This meager diffuse staining is less than that which one usually finds in moribund tissue which has been subjected to the action of trypan blue intra vitam. In showing an entire absence of dye granules these leukocytes are quite similar to the few polymorphonuclears which were found in the aseptic brain injuries and in the area of inflammation in Macklin's fracture cases. It may be, as would be suggested by the work of Downey,[14] that the polymorphonuclears did take up

14. Downey, H.: Further Studies on the Reactions of Blood- and Tissue-Cells to Acid Colloidal Dyes, Anat. Record **15**:103, 1918. Reactions of Blood and Tissue Cells to Acid Colloidal Dyes Under Experimental Conditions, Anat. Rec. **12**:429, 1917.

the dye in quantity, holding it in granular form, during the first hour or so, and later allowed it to diffuse out. To settle this point we would have to examine the abscess very soon after staining with trypan blue. But even admitting this to have occurred, would not such an early ingress of the dye into the polymorphonuclear, followed by its almost immediate egress therefrom, constitute a most important physiologic distinction as compared with the macrophage, which not only is slower in taking up the dye (according to Downey) but retains it in granular form for a very much longer time? Is it not probable, too, that this very decided functional difference in reaction to trypan blue and similar substances is to be accounted for by the peculiarities of structure which these cells show—we might even say largely by the equipment of the macrophages with their innumerable vacuoles, analogous, as Shipley[4] has pointed out, to the food vacuoles of the protozoa? We would emphasize as important the fact that the two cell types show such an enormous difference in respect to their reaction to trypan blue under the conditions of our experiments—a difference in keeping with the other evidences of functional separateness which these cells show, such as the tremendous enlargement which the macrophage undergoes in consequence of its enormous intake of foreign material, in contrast to the practical absence of hypertrophy on the part of the polymorphonuclear cell. The attempt to account for such marked disparity in behavior on the ground of "availability of the dye," as Downey[14] suggests, seems inadequate, to say the least, when one considers that vitally stained macrophages are often found scattered among polymorphonuclears which contain no dye granules in an intimacy of juxtaposition that leaves no reason for concluding that the dye is any more available to the one cell type than to the other.

While it is undoubtedly true, as Downey[14] has repeatedly shown, that dye aggregations can be made to occur in polymorphonuclear leukocytes by subjecting them to very high concentrations of dye and unfavorable environment, as within a doubly ligated vein, or in the stagnated blood of an animal that died some time before the material was taken from it for examination, yet this method can hardly be looked on as tending to bring out the distinctive characters of these cells, as contrasted with the macrophages. Rather it is likely to reduce them to a common dead level, due to the toxic action of the dye (an action which Downey[14] admits—p. 123), when exhibited in such excessive amounts; and in considering Downey's leukocytes with their stained granules, one cannot help recalling the experiment of Evans and Schulemann,[15] of which the substance is contained in their quota-

15. Evans, H. M., and Schulemann, Werner: The Action of Vital Stains Belonging to the Benzidine Group, Science, N. S. **39**:443, 1914.

tion (p. 10): "When we tap the cover slip over leukocytes swimming in trypan-blue, mechanical injury to the immediate subjacent cells invites instant entry of the dye."

Cold Stabs.—As a comparison with the hot stabs a number of rats were operated on by simply stabbing the brain with a sterile cold needle, the rest of the technic being similar to that of S27. The tissue damage, of course, was much less, and thus there was but little diffuse staining. Macrophages of the same type and of similar size (by actual measurement) were present, but their numbers were less. In a given volume of damaged tissue, however, they seemed to be as numerous as in the hot stabs. Their vital staining was in all respects similar to that of the phagocytes of the hot stabs.

Fresh Material.—In a number of cases (not included in the table of material) we studied these brain macrophages in the fresh tissue, in some cases from vitally stained animals, and in others from animals simply operated on without staining. The operative and staining technic was the same as that in S27. Our interest centered principally around the dye and fat content. Most of the cases were examined on the third day, when the phagocytes are at the height of their activity. The latest stage examined was the eighth day. Immediately after being killed by bleeding, under ether anesthesia, the brains were dissected out and at once placed in normal Locke's solution at 37 C. Bits of tissue from the wound area were teased out on a slide and kept on the warm stage during the examination. In those animals which had received the vital dye the macrophages were plainly evident by reason of their dye content. They seemed to contain no more than in the fixed preparations. Sudan III was then added to the preparation and the cells appeared filled with large orange colored droplets. Many similar droplets were floating about free in the surrounding fluid. The treatment with sudan III, however, tended to decolorize the dye. This is doubtless due to its alkalinity. The same brilliant staining with sudan III was, of course, obtained in the animals which had received no dye. Some of the teased preparations gave most interesting results, for it was easy to separate the long slender capillaries which are so prominent during the early stages of repair. Lining these tiny vessels were to be found numerous protuberances, which stained with sudan III, and were quite evidently macrophages attached to their walls. The walls themselves contained globules of stained fat, and some of these were even present in the lumen, suggesting strongly a passage of the fat into the vessels—a process in which the macrophages may play a part, for they are ameboid, and it is not difficult to think of them as gathering their load of fat and carrying it to the vessels, into which they deliver it. A somewhat analogous relation-

ship has been described by the Clarks[16] for leukocytes and lymphatic sprouts in the transparent tails of tadpoles, which suggests the well-known hypothetical action of the leukocyte in fat absorption from the intestine. Irrespective of such a speculation as to the action of the macrophage in fat absorption from brain lesions, the taking up of fats and other materials from such areas by the blood vessels appears to be pretty certain, for the subarachnoid spaces do not seem to receive much of these waste products, and the ventricular system apparently is not, in these aseptic cases, an important pathway for the exit of these substances. The important rôle which the blood vessels play in the removal of exudate has been recognized for some time. Recently Shipley and Cunningham,[17] in their valuable work on the taking up and removal of fine particulate matter and colloidal and molecular solutions from the peritoneal cavity, have demonstrated that this function is carried on largely by the blood vessels of the omentum. Downey,[14] too, has found evidence that the blood vessels of the subcutaneous connective tissues may drain away foreign materials. Such an action on the part of the young vascular sprouts of brain lesions is only what we might expect, and it seems probable that the increased staining with trypan blue which we noted in the larger vessels in the region of the injury may be part of the same functional adaptation. Since the process of fat absorption extends over quite a long period it is not likely that the fat content of the blood is appreciably raised above normal at any time. It is interesting to note that Coen,[7] at the second day of repair of similar brain injuries, noted fat droplets in what he terms lymph vessels, and also in perivascular spaces.

Frozen sections stained with sudan III gave similar pictures to those from fresh teased material, though not so striking, for not such long stretches of the vessels could be isolated. Many of these cells are undoubtedly modified endothelium. Of course, a great many phagocytes were detached from the vessels—indeed it is probable that most of them were. In preparations stained with osmic acid the same relationship of fat-containing phagocytes to the vessels was obtained. Nile blue sulphate was used, both with the fresh tissues and frozen sections, but the results obtained were unsatisfactory, for this dye was found not to be specific for fat, and so did not serve to differentiate it as did the sudan III.

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16. Clark, Eliot R., and Clark, Eleanor Linton: A Study of the Reaction of Lymphatic Endothelium and of Leukocytes, in the Tadpole's Tail, Toward Injected Fat, Am. J. of Anat. **21**: 421, 1917.

17. Shipley, P. G., and Cunningham, R. S.: Studies on Absorption from Serous Cavities. I. The Omentum as a Factor in Absorption from the Peritoneal Cavity, Am. J. Physiol. **40**:75, 1916. II. The Histology of Blood and Lymphatic Vessels During the passage of Foreign Fluids Through Their Walls, Anat. Rec. **11**:181, 1916.

Pia-Arachnoid Cells.—We have referred, in the description of the gross specimens, and again when speaking of the staining of macrophages, to certain of the cells of the pia-arachnoid membrane which, in the vicinity of the lesion, show a propensity for dye ingestion and storage. They are found in the infoldings of pia near the lesion, as well as on the exposed surfaces. We have described them as occurring almost constantly in S27, from the sixth hour to the sixth day, and from that time intermittently up to the twenty-fourth day. They were present in a depressed fracture case on the fourth day. In the matter of dye ingestion these cells were somewhat more precocious than the brain phagocytes; they also differ in taking up more dye, and so appear more conspicuously stained than do the "Körnchenzellen." In shape they show a tendency toward oval and elongated forms. Dye was often found clumped in grayish-blue masses half as large as the cell, and, in considering the cells of the vicinity of the lesion one cannot escape the impression, especially in the stages immediately following the injury, that the cells are seriously damaged, and so absorb the dye, rather than that they take it up by reason of their phagocytic activities. The latter are undoubtedly operative in the cells more remotely situated from the lesion, however, and in the later stages, for typical dye granules are found in them. Appropriate stains demonstrated the presence of fat globules in these pia-arachnoid cells. In the microscopic sections dye was first found at the end of one day.

Although it seems probable that some of the diffusible products of inflammation find their way into the subarachnoid space, especially in the early stages, yet the rarity of occurrence of dye-reacting cells in the membranes at any distance from the lesion points, in our mind, to but a very slight contamination of this interval. Doubtless the function of the cells here is to ingest any toxic materials which may enter. The cells of the pia proper show this reaction, and dura cells in the wound precinct manifest the same increase in dye ingestion. To them a similar function may be ascribed.

Choroid Plexus.—We have mentioned, in the description of the gross material, that the choroid plexus, from the first hour to the sixth day, was more intensely stained on the side of the lesion than on the opposite side. Normally, as is well known, the choroid plexus shows, in animals vitally stained with trypan blue, a distinct coloration. This is to be found in certain "secretory granules" of the choroidal ependyma (Evans and Schulemann[18]) but especially in the bodies of the macrophages, a number of which are always found in the plexus. It is in these cells that most of the dye is stored.

It would appear that, in the early stages, say the first twenty-four hours, the ipsilateral plexus shows an increased staining on account of

its having been injured. However, it is noteworthy that the sections from the injured side soon show in the regular macrophages (first, second and third day stages) an increase in dye content (Fig. 28) as compared with those of the contralateral side, and it seems evident that these cells play a part in ingesting the excreta of the wound area. They did not show this increase after the fourth day. They contained fat globules in abundance. When the ventricle is penetrated, of course, the reaction of these cells is most marked, and much foreign material finds its way into the ventricular system. Even when the lesion does not involve the ventricle, but is situated close to it, we feel that some waste material may diffuse into it. We have, in the osmic preparations, found numerous globules of fat in the lateral ventricle, and it would seem that this space may become a drainage pathway for exudate arising in the adjacent parts of the cerebral hemisphere. However, the amount of material entering the unwounded ventricle, in our experience, was slight. Interesting in this connection are the observations of Essick,[10] who has shown that infections of the brain spread without difficulty from the lesion into the ventricle, and one gathers from his account that the ventricular system is more vulnerable, in this respect, than is the subarachnoid space.

The macrophages of the pia-arachnoid and of the choroid plexus must, therefore, be regarded as cooperating with those developing in the brain substance in dealing with diffusible effluxions from the inflammation focus.

In the healing of the wounds of skin, skull and dura, macrophages play a similar part, early rallying to the field and showing marked trypanophilic tendencies, as Macklin[2] has shown.

SUMMARY

The general features of the healing of aseptic lesions of the brain as brought out in this investigation may be briefly summarized. The defunct tissue is rapidly absorbed, and this is accomplished by a temporary cellular mechanism, made up of young blood vessels, phagocytes and connective tissue——in fact, a granulation tissue. This, in turn, gives place to a rather light scar. There is noted very early a separation of the irreparably damaged tissue from that reparably damaged —a separation at first indicated by a zone of ameboid mononuclear phagocytes, and later accomplished by a membrane of connective tissue which is continuous above with the leptomeninges, and is joined by strands of connective tissue with the reticulum which comes to occupy the defect. Repair of the brain tissue immediately surrounding this isolating membrane is not complete, and its essential composition, although not altogether destroyed, is profoundly changed. There is often an apparently insoluble residue of tissue which persists in the

defect for two months or more; this, however, is very scanty. Red cell absorption was rather slow in these cases. An attempt is made to obliterate the defect, but this is often imperfect.

When foreign tissue was transplanted into the lesions there was some delay in healing. Delay was also noted when the exposure of the animal to trypan blue was prolonged.

Fully developed macrophages were present in the lesion in all stages from the second to the seventy-fourth day. Their period of most intense activity appeared to be from the second to about the sixth day, or shortly after. Though their sizes showed great variation, ranging from 7 microns to 42.7 microns, the average long diameter was found to be 13.6 microns.

The wound area, caused by stabbing with a hot needle, in the brains of rats into whom trypan blue has been introduced two days before death, presents a characteristic picture. As was to be expected, the dead tissue (both that which was homogeneously coagulated by the heat and the cells which still retain something of their morphology) is diffusely and deeply stained blue. Often the cells take up more dye than the intercellular material. This staining lasted from before the first hour to about the tenth day. It gradually became faint, as the stainable substance diffused out. Similar staining was found in cerebral lesions produced by other methods.

In the coagulated tissue in the early stages (six-hour to three-day) there were found granules which looked like the "dye granules" found in the cytoplasm of the macrophages. They are probably stained masses of protein decomposition products which have absorbed and concentrated the dye. They were also found in the coagulum at the eleventh and fifteenth days, where staining was of long duration.

Around the lesion in the early stages was an area of pale blue, probably the site of an inflammatory edema. This also occurred in concussion and depressed fracture cases, and in meningeal infection.

The superficial blood vessels of the injured side were more heavily stained than those of the other—perhaps denoting an increased permeability. In the inflamed tissue vitally stained phagocytes were found lying along the blood vessels and even composing part of their walls.

Vitally stained mononuclear cells appeared in the inflamed region at the end of the second day and disappeared by the sixth day, or shortly thereafter. They contained much lipoid material. The fat droplets and dye granules seem to occupy separate protoplasmic compartments. Blood pigment is found in cytoplasm also, being most abundant about the fifteenth day. Rarely are entire corpuscles found within the cells. As compared with macrophages occurring in wounds of other tissues these cells were remarkable for the small amount of dye they took up, and the short duration of their staining, when

exposed to the dye for forty-eight hours. Then, too, in the brain cases many phagocytes contained no dye, whereas in the fracture cases practically all contained dye. This marked difference in response of brain macrophages toward trypan blue as compared with those occurring in other tissues is in all probability due to the larger amount of fat in which they are situated. Apparently these brain macrophages display phagocytic activity toward fat and blood pigment long after they cease to respond to the dye when exhibited for a period of forty-eight hours. Similar phagocytes appeared in the pia-arachnoid membrane around the lesion. They took the dye a little more avidly and somewhat earlier than the macrophages in the brain tissue.

If animals operated on were allowed to live for from eleven to fifteen days after injection of the dye, the macrophages were quite deeply stained. Such prolonged staining, however, seemed toxic to the animals, as evidenced by the high mortality. It inhibited to a very marked degree the absorption of the waste material, and delayed healing.

The macrophages of the brain lesions differed also from similar cells occurring in other tissues in that no transitional cells from lymphocytes were found, and that they multiplied by mitosis at the site of injury. They were apparently recruited in part from the neuroglia, for hypertrophied neuroglia cells containing dye granules and other material were found in the area of inflammation. Some also arise from the endothelium of the blood vessels, for endothelial cells in the injured region became enlarged and filled with foreign material. They then behave like the other macrophages. By careful dissection of the fresh or formaldehyd-fixed specimens, capillaries lined by large fat endothelial phagocytes may easily be isolated. These may also be found in the sections. It is possible that the cells of the pia-arachnoid, growing down into the wound, and adventitia cells from the ingrowing blood vessels, add their quota to the phagocytes, as found by several workers.

In a small abscess of the brain the wall was composed mainly of large macrophages. These stained very brilliantly with trypan blue—much more so than the brain macrophages of the aseptic cases at any period. They resembled closely the macrophages about fractures. This abscess specimen was examined at the twelfth day—a stage when no dye was found in the ordinary brain macrophages. This circumstance suggests that the type of material absorbed may have something to do with the positive reaction of the macrophage toward the vital dye. No dye granules were found in the polymorphonuclear leukocytes of the abscess.

Introduction into the brain lesions of other tissue material, such as liver, spleen, muscle, etc., in an effort to attract macrophages similar to those of inflammatory lesions in other tissues (i. e., cells that would

take up more dye, and exhibit developmental forms arising from lymphocyte-like cells) gave negative results.

The function of the macrophages apparently is to ingest the products of tissue decomposition. It appears that they subject these products to a form of digestion (Shipley[4]). It is even suggested that fat may be transported by the macrophages to minute blood vessels, through the walls of which the globules pass, to be finally carried off in the blood stream. In any event, the greater amount of absorption of waste materials from the wound site seems to take place via the blood stream, although a little doubtless diffuses into the adjoining subarachnoid space and lateral ventricle.

The macrophages are incorporated in the scar formed by the fibroblasts, although there is no evidence in this work that they actually proliferate to form that scar. Some were found in the defect more than two months after the operation.

Cells of the dura about the lesion became phagocytic, and responded to the dye to some extent. The macrophages of the choroid plexus became more responsive to the dye than normal during the first three or four days of the injury.

Failure of a cell to respond to the vital dye cannot be held to exclude it from the possession of phagocytic activity, since the same cell early in its history may take up the dye, and later fail to do so, while at the same time continuing to ingest fat, blood pigment and other substances. Again, in some cell groups, many of the macrophages may contain no dye (and yet presumably be phagocytic, as evidenced by their content of ingested material) while others, right beside them, contain dye in appreciable quantities. Whether or not a cell contains visible dye granules, however, depends largely on the amount of dye given and the duration of the staining, as the special cases of prolonged staining show. Thus vital staining should be used with discretion as a macrophage indicator, as it is not always an infallible criterion.

Cold stabs showed no essential difference as compared with the hot stabs except the much slighter extent of the injury.

In conclusion, we wish to express our thanks to Dr. Streeter, Director of the Carnegie Laboratory of Embryology, for laboratory facilities and assistance with the illustrations generously granted.

Explanation of Plate 1

Fig. 1.—Crayon drawing of brain of white rat which has been stabbed with a red-hot needle, and killed twelve hours after operation. Trypan blue, 4 c.c. intraperitoneally in 1 per cent. aqueous solution forty-eight hours before death, with a second dose of 4 c.c. twenty-four hours before death; S27-23, twelve-hour stage. Note intense blue of central necrotized area, surrounded by a zone of paler blue. Superficial blood vessels of injured side stain more intensely than those on the other side. The staining of pineal body is normal. This brain was cut transversely along the stab, and the cut surface is shown in Figure 3. ×2; drawn by B. E. Stocking.

Fig. 2.—Crayon drawing of brain of rat. Similar operation and staining to that of brain shown in Figure 1, but drawn from the six-day stage of repair; S27-14. The intense blue staining of the necrotized tissue persists, but the surrounding paler zone has diminished in size and in intensity of color. The superficial blood vessels still show more intense staining on the injured side. A cross section of the stab, from a cleared slice of tissue, is shown in Figure 4, and cleared longitudinal sections of it are seen in Figures 5 and 6. ×2; drawn by B. E. Stocking.

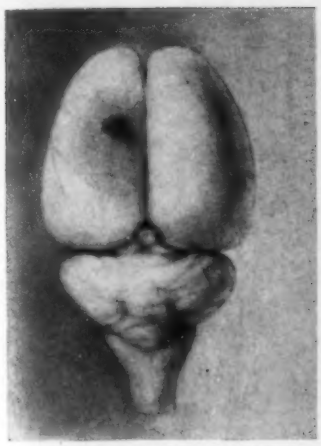
Fig. 3.—Crayon drawing of transverse section through the brain from which Figure 1 was drawn, showing a longitudinal section of the stab—S27-23; twelve-hour stage. The dense blue coagulated central plug is sharply marked off from the lighter blue zone surrounding it. ×2; drawn by E. Lovett.

Fig. 4.—Water-color-crayon drawing of thick slice cut transversely to the stab from the brain shown in Figure 2. Specimen cleared in oil of wintergreen and drawn under the binocular microscope—S27-14; six-day stage. Note the densely and diffusely stained coagulum occupying the center; around it is the paler intermediate zone. Next we see the necrotic wall, its inner margin appearing as a thin blue ring. The dye in this ring is partly in granule form, in the bodies of macrophages, and partly in a diffuse staining of the young connective tissue which is gathering here, and which represents the beginning of the membrane that will wall off the defect. The diffuse staining of the remains of the necrotized tissue also probably contributes to the blue color. Conspicuous in the surrounding inflamed tissue are the numerous blue granules, which represent dead nerve cells, as well as a few macrophages which contain vital dye. In the sections of the six-day stage there was very little intramacrophagic dye. The radiating blue lines are blood vessels, which appear so not only because their walls stain diffusely (more intensely than normal vessels) but also because their endothelial cells, and macrophages applied to their walls, contain dye. Similar vessels run upward toward the meninges, as seen in Figure 6, from the same specimen. There are some masses of extravasated blood. ×20; drawn by E. Lovett.

Fig. 5.—Water-color-crayon drawing of a slab, cleared in oil, cut transversely from the brain seen in Figure 2. This shows a stained lesion, as seen with the low power of the binocular—S27-14; six-day stage. The blue staining of the lesion is conspicuous, but the zones are not so well marked as in the uncleared specimens. The staining of the choroid plexus on the injured side is greater than that on the other side. The enclosed area is shown more highly magnified in Figure 6. A cross-section of this stab, made by placing the two halves together, is seen in Figure 4. ×4; drawn by E. Lovett.

Fig. 6.—Water-color-crayon drawing of a small area from Figure 5 (shown enclosed) as seen under the high power of the binocular—S27-14; six-day stage. The granular nature of the staining is due to dead ganglion and other cells, as well as to vitally stained macrophages. The amount of dye within the cells, as shown by sections, is slight. Again (as in Figure 4) we find blue lines, representing blood vessels. Here they are mainly running up to the meninges. ×44; drawn by E. Lovett.

PLATE 1



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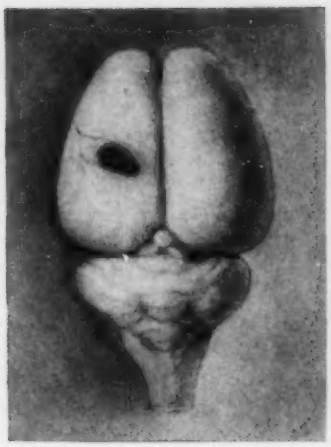

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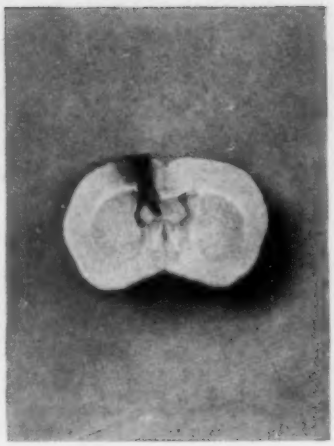

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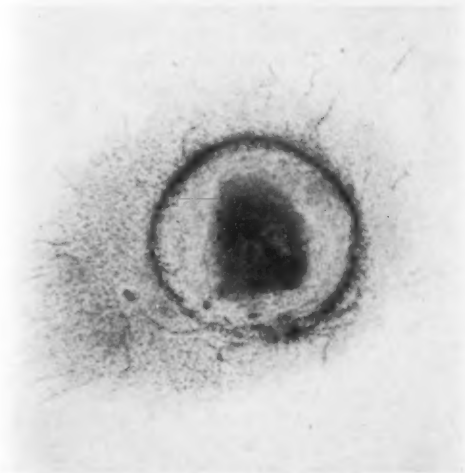

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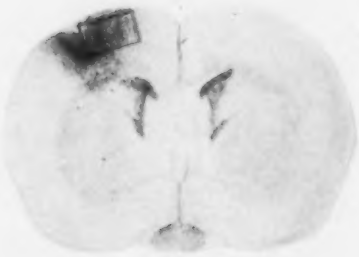

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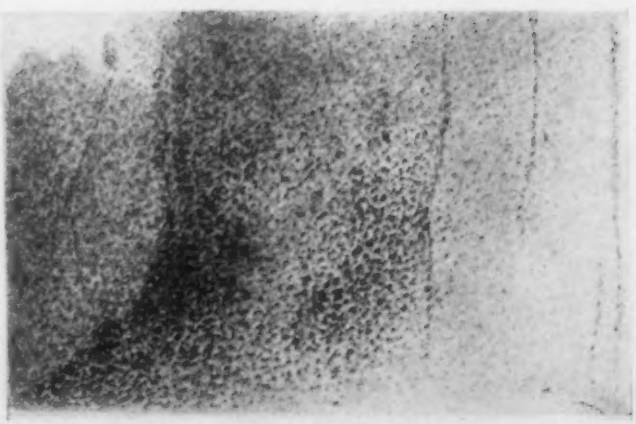

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Explanation of Plate 2

Fig. 7.—Water-color drawing of the abscess shown in Figure 22 as a photomicrograph—S27-41; twelve-day stage. The drawing was made from a thick section, simply cleared without counterstaining. The rather pale, diffuse blue area in the center is occupied by the pus cell accumulation, with the remains of the necrotized tissue. The conspicuous blue granular ring is due to the vital dye in the host of macrophages composing the envelope of the abscess. A section of the wall is seen in Figure 25, and a group of macrophages from it in Figure 23. ×80; drawn free-hand by S. E. Watson.

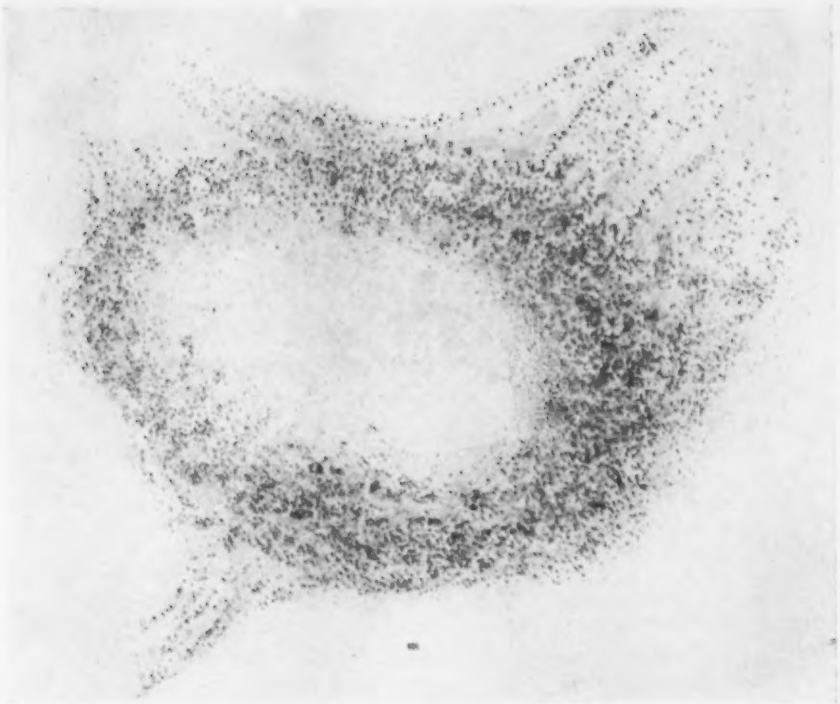
Fig. 8.—Water-color drawing of two macrophages found in the dead tissue of the two-day stage—S27-6-9; light counterstaining with carmin. Note the granules of trypan blue. These were particularly well stained cells, the vast majority containing less dye, or none at all. Figure 13 presents a photomicrograph of this stab, and in Figure 24 are seen macrophages from the peripheral region of the same specimen. Camera lucida with Leitz 2 mm. oil immersion lens and No. 6 compens; ocular; ×1500; drawn by M. T. M.

Fig. 9.—Water-color drawing of two macrophages from the edge of the coagulum at the three-day stage—S27-37-4; lightly counterstained with carmin. These, too, were selected because they contained more dye than most of the others. They are not quite so well stained as those of the two-day stage, shown in Figure 8. They were surrounded by red blood cells and other macrophages containing no trypan blue. Photomicrograph of this stab is seen in Figure 14. Camera lucida and oil immersion lens; ×1500; drawn by M. T. M.

Fig. 10.—Water-color drawing of a very large phagocyte found in the lesion at the fifteen-day stage—S27-18-8; hematoxylin and eosin stain. The cell contains no vital dye, and its cytoplasm is made up largely of a host of vacuoles. Its size may be estimated by the red blood cells around it. In Figure 15 a photomicrograph of the stab is seen. Camera lucida and oil immersion lens; ×1500; drawn by M. T. M.

Fig. 11.—Water-color drawing of similar cells from the lesion of the same specimen—S27-18-5; fifteen-day stage. Hematoxylin and eosin stain. These cells are particularly noteworthy for their content of blood pigment. Note size of red blood cells. Section of stab is seen in Figure 15. Camera lucida and oil immersion lens; ×1500; drawn by M. T. M.

PLATE 2



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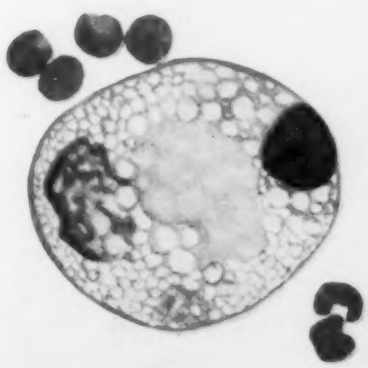

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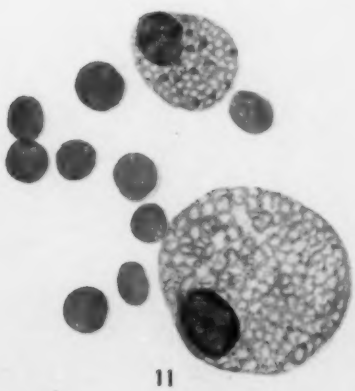

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Explanation of Plate 3

Fig. 12.—Photomicrograph of a longitudinal section of the stab at the six-hour stage — S27-24-6; hematoxylin and eosin stain. The dark strip in the center is the coagulum. Running through it is the cleft made by the needle, and it contains many small blood clots. Its dark appearance is due largely to the dye which it has absorbed. Around this coagulated tissue is the intermediate zone, lighter in tone, and open in texture. Outside of this, again, is the more or less necrotized wall of the brain tissue, which passes gradually into the normal brain beyond; × 60.

Fig. 13.—Photomicrograph from a similar preparation, only at the two-day stage of repair — S27-6-7; hematoxylin and eosin stain. The coagulum, with its blood clot, is seen occupying the center, and around it are the zones already described. The phagocytes, which are invading the field, are not seen in the figure. Two of them are shown in Figure 8, from the edge of the coagulum. The cross in the upper right-hand corner marks the spot from which Figure 24 was drawn. Macrophages are found all through this region. Peculiar extracellular dye granules are found in the coagulum, as shown in Figure 27; × 60.

Fig. 14.—Photomicrograph showing the split stab at the third day of repair—S27-37-6; hematoxylin and eosin stain. The zones are well shown. The most interesting feature is the enormous number of phagocytes in the intermediate zone. Two of these appear in Figure 9. Only the nuclei appear in the illustration. There is some solution of the necrotic tissue. A membrane, isolating the defect from the surrounding brain tissue, will later appear in this region of phagocytic concentration, as the next figure will show; × 60.

Fig. 15.—Photomicrograph showing the split stab at the fifteenth day of repair — S27-18-5; hematoxylin and eosin stain. Note that in this specimen, where the injury was relatively slight, the necrotic tissue has almost entirely been removed, leaving a loose reticulum, in which are a few macrophages. Figures 10 and 11 were drawn from this area. Note the membrane, continuous above with the pia-arachnoid, which cuts off the surviving brain tissue from the defect; × 60.

PLATE 3

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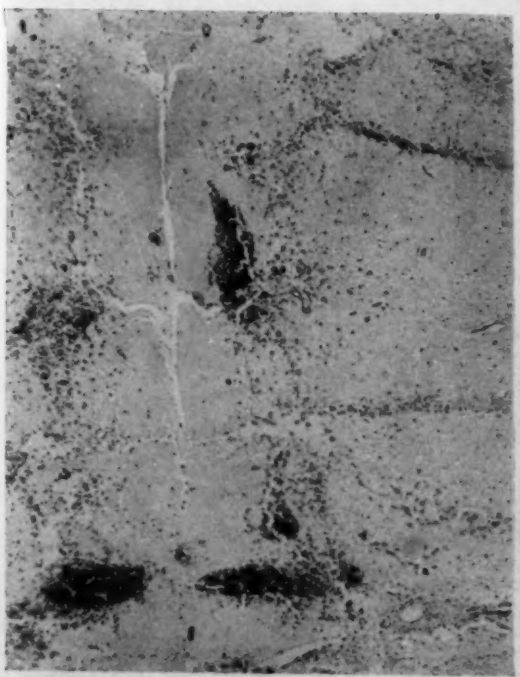

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Explanation of Plate 4

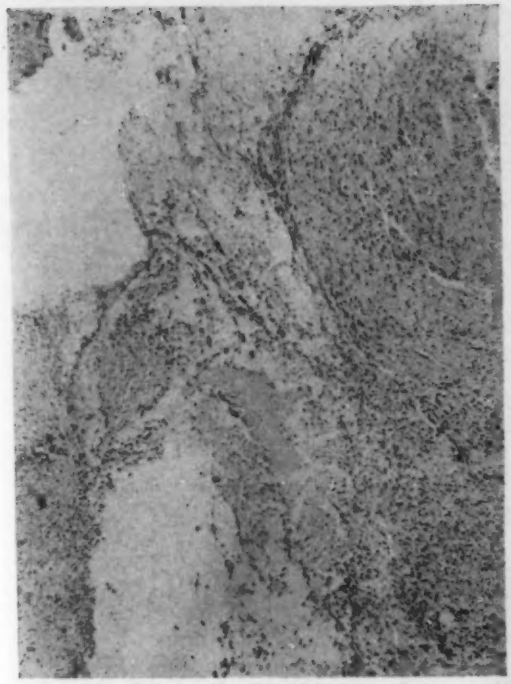
Fig. 16.—Photomicrograph of the split stab at the twenty-fourth day—S27-46-1; hematoxylin and eosin stain. This was a more severe injury than that of Figure 15. The defect is marked by open spaces and the remains of the necrotized tissue, with a reticulum of connective tissue and blood vessels in places. Many macrophages persist, as the next figure shows. Note the membrane which delimits the injured region. It is best marked above; × 60.

Fig. 17.—Photomicrograph of an area from Figure 16, at a higher magnification. Twenty-four-day stage— S27-46-1; hematoxylin and eosin stain. A number of large macrophages are seen. Below is the brain wall, with a short length of the isolating membrane; × 280.

Fig. 18.—Photomicrograph of the defect at the sixty-second day — S27-3-4; hematoxylin and eosin stain. A loose reticulum of connective tissue, and a few shreds of apparently indissoluble coagula, occupy it. The isolating membrane is well marked, and is seen in the next figure more highly magnified. A few macrophages persist; × 60.

Fig. 19.—Photomicrograph of the membrane lining the wall of the defect seen in Figure 18 — S27-3-4; sixty-second day stage; hematoxylin and eosin. The surrounding brain wall is open and reticulated in structure, and the large nerve cells have been destroyed. A few macrophages are seen; × 280.

PLATE 4



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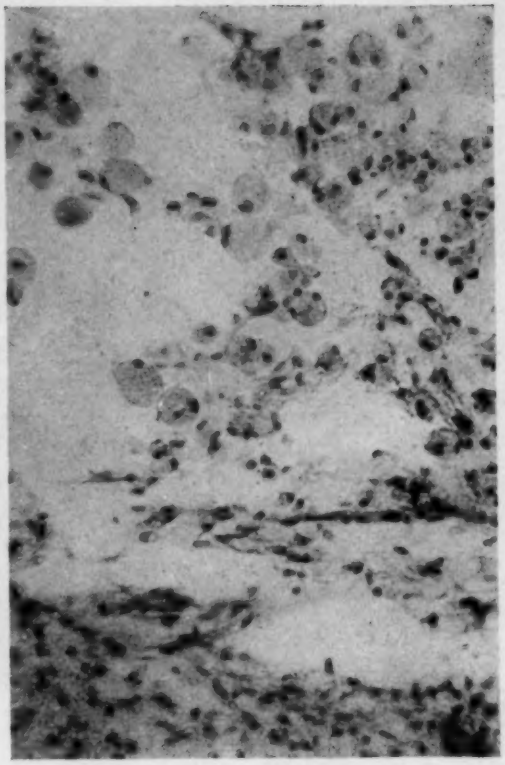

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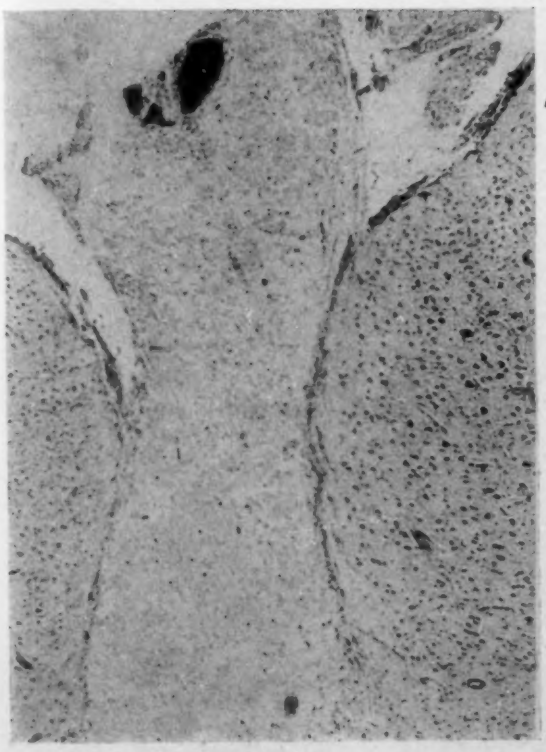

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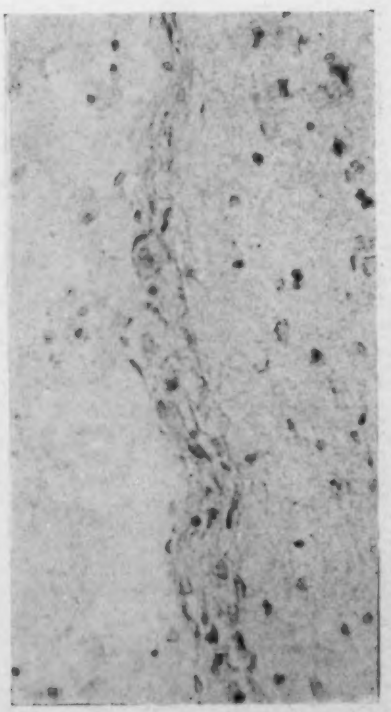

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Explanation of Plate 5

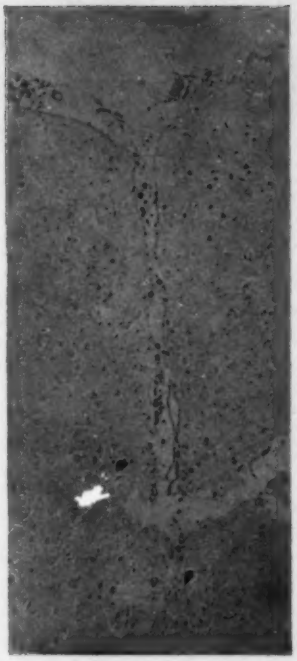
Fig. 20.—Photomicrograph of the stab at the seventy-fourth day of repair—S27-4-4; carmin stain. This injury was made by a slender needle, and was relatively slight. The defect is comparatively trivial. In the thin cleft are a number of pigment containing macrophages, and the limiting membrane is much attenuated. The next figure shows it at a higher magnification; × 60.

Fig. 21.—Photomicrograph of the top of the specimen seen in Figure 20—S27-4-4; seventy-four-day stage; carmin stain. Note the few macrophages in the defect; × 280.

Fig. 22.—Photomicrograph of small abscess which was found at the twelfth day of repair in one of the S27 cases (S27-41-9); carmin stain. The pus cell accumulation is shown walled in by macrophagic tissue, beyond which is a zone of fibrous tissue, cutting off the brain substance. The area enclosed is seen enlarged in Figure 25. Figure 7 shows this abscess as it appears in the cleared and uncounterstained section, and exhibits the dye content of the macrophagic wall. In Figure 23 a group of macrophages from this wall appears at a higher magnification; × 60.

Fig. 23.—Wash drawing of a group of macrophages from the wall of the abscess shown in Figures 22 and 25—S27-41; twelve-day stage; carmin stain. Dye granules are seen in jet black in the drawing, but appear blue in the original specimen. Camera lucida; × 780; drawn by M. T. M.

PLATE 5



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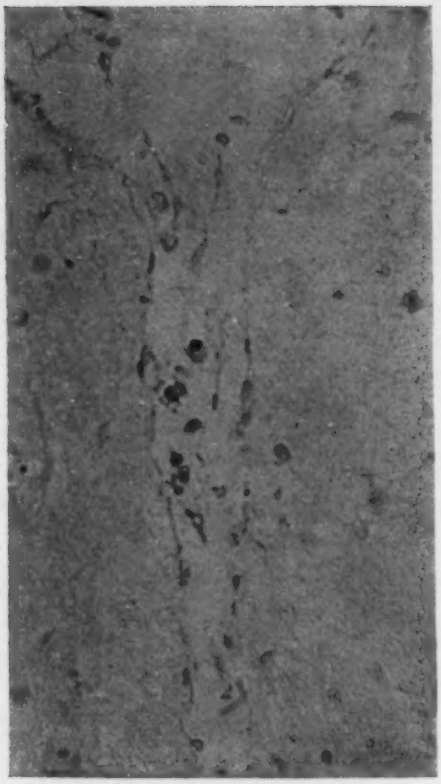

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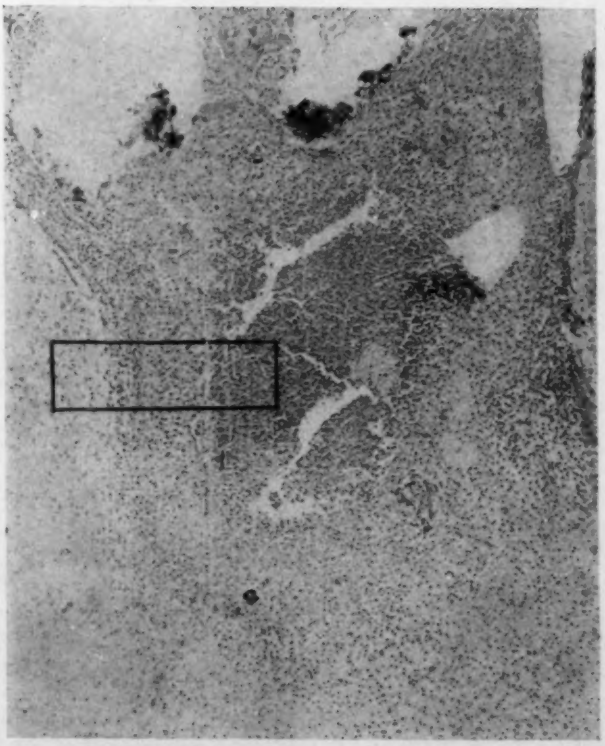

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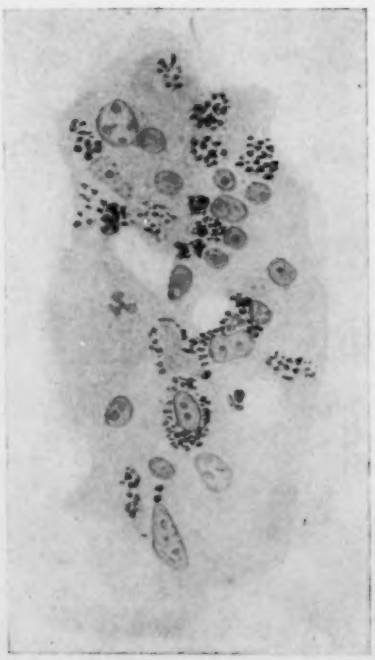

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Explanation of Plate 6

Fig. 24.—Wash drawing of an area of brain tissue from the two-day stage (region shown by cross in Figure 13)— S27-6-6; carmin stain. The tissue has been damaged by the heating, and the ganglion cells are dead. They appear in the drawing as irregular dark masses. A few of the neuroglia cells have taken the vital staining, and contain bright blue granules in the original specimen. These granules are shown in the drawing as jet black. Note the reticulated appearance of the intercellular substance. Camera lucida; × 780; drawn by M. T. M.

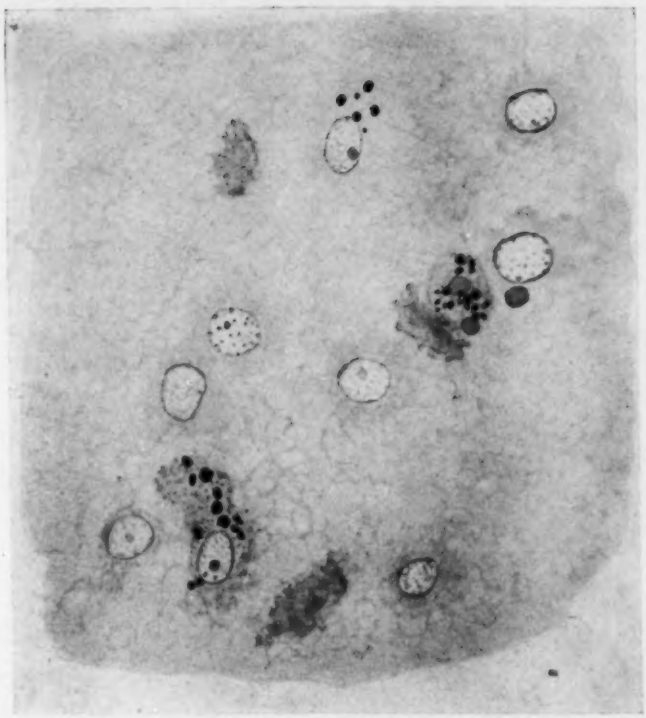
Fig. 25. Wash drawing of a panel from the abscess shown as a photomicrograph in Figure 22; S27-41-9; twelve-day stage; carmin stain. From below up we have the pus cell accumulation (*a*); the macrophage wall, with dye granules shown in jet black (*b*); the fibrous membrane (*c*); and the surrounding brain (*d*). Some of the macrophages are shown more highly magnified in Figure 23. Camera lucida; × 340; drawn by M. T. M.

Fig. 26.—Wash drawing of arachnoid, subarachnoid space, pia and underlying brain, from an area near stab, at the second day of repair—S27-6-6; carmin stain. A stab of this specimen is seen in the photomicrograph, Figure 13. Two pia cells are shown somewhat enlarged, and contain dye, which is depicted as jet black granules. Camera lucida; × 780; drawn by M. T. M.

Fig. 27.—Crayon drawing of an area of coagulum in which small dye granules of varying size appear (shown in jet black). Section cleared without counterstaining—S27-6; two-day stage. In the original the background is of pale diffuse blue, while the granules are strongly blue. The intensity of staining of the granule varies. Some of the granules are in small clumps. A few red blood cells are seen. A photomicrograph of this stab appears in Figure 13. Camera lucida; × 1500; drawn by C. C. M.

Fig. 28.—Wash drawing of a frond of the choroid plexus on the injured side at the second day of repair—S27-6-6; carmin stain. The same specimen is shown in the photomicrograph in Figure 13. The macrophages are found densely stained with dye granules; three are seen in the figure. A few stained granules in the epithelium appear also. All dye granules are shown in jet black. Camera lucida; × 780; drawn by M. T. M.

PLATE 6



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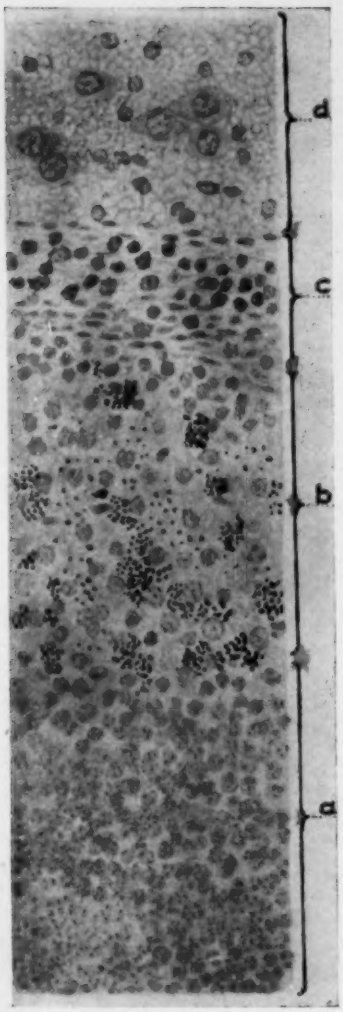

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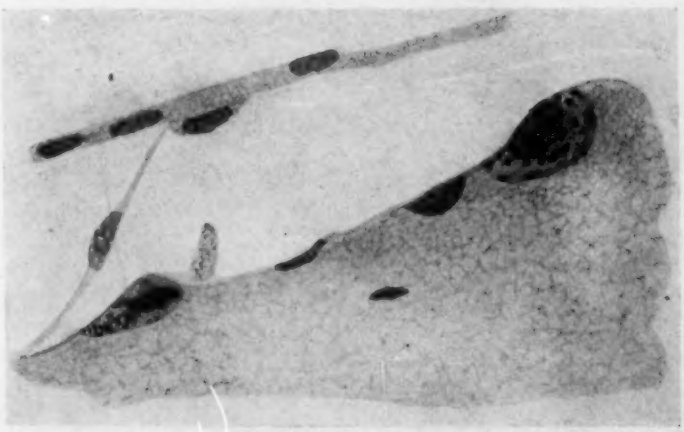

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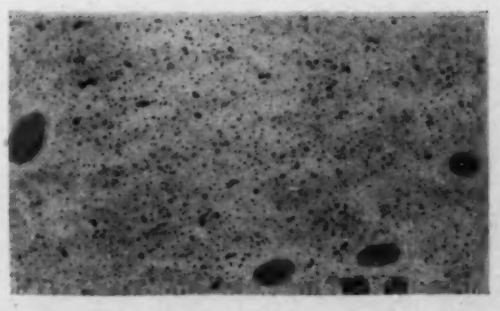

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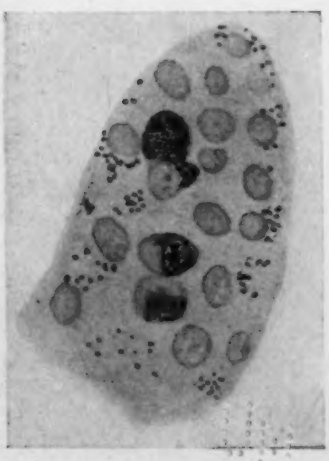

28

A CASE PRESENTING AN EPIDERMOID PAPILLARY CYSTOMA INVOLVING THE THIRD VENTRICLE *

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GENERAL NEUROPATHOLOGY OF THE CASE

Epidermoid growths involving the third ventricle have created particular interest with reference to their relation to the pituitary body and the disturbance of its function, the possibility of localization of such tumors, and their source of origin.

Recalling the epiblastic origin of the neural tube, one is not surprised to find in close relation to the central nervous system, ectodermic cells originally intended for skin and mucous membrane. They may develop as if they were in their normal location with the formation of dermoid cysts or cholesteatomas.

The presence of epidermoid tissue in the third ventricle may be explained as being the result of an infundibular anlage. Cushing[1] reports two examples of infundibular cysts filled with a yellowish gelatinous substance, and with numerous verrucose nodules composed of squamous epithelium projecting from the walls, which he considers as possible developmental aberrations in relation to the neurohypophysis. Similar infundibular cysts were described by Langer[2] and Strada.[3]

Saxer[4] reported a tumor which he believed originated from the epithelial lining of the ventricle, or the pars intermedia of the pituitary body, the gland being normal.

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* From the Massachusetts State Psychiatric Institute, Massachusetts Commission on Mental Diseases. This paper was one of a series presented to Dr. E. E. Southard on the occasion of the tenth anniversary of the establishment of the Bullard Professorship of Neuropathology, Harvard Medical School, 1906 to 1916.

1. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, p. 289.
2. Langer, F.: Ueber Cystische Tumoren im Bereiche des Infundibulum Cerebri, Ztschr. f. Heilk. **13**:57, 83, 1892.
3. Strada, F.: Beiträge zur Kentniss der Geschwülste der Hypophyse und der Hypophysengegend, Virchows Arch. f. path. Anat. **203**:1, 1911.
4. Saxer, F.: Zeiglers Beiträge **32**:333, 1902.

Mott[5] mentions the possibility of epidermoid tissue being transported by the vessels which grew into the third ventricle to form the choroid plexus, also of its having arisen from cells of the hypophyseal diverticulum.

The hypophysis or anterior lobe of the pituitary body originates as a pharyngeal diverticulum (Fig. 1). The exact location of its origin with reference to the juncture of the pharyngeal and buccal epithelium is still a matter of dispute. Minot[6] considered the diverticulum an outgrowth from the ectodermal lining of the mouth. Normally, the cells forming the original stalk atrophy and the hypophysis loses all connection with the epithelium of the oral cavity. It is not uncommon, however, to have a retention of some cells along the stalk tract, and

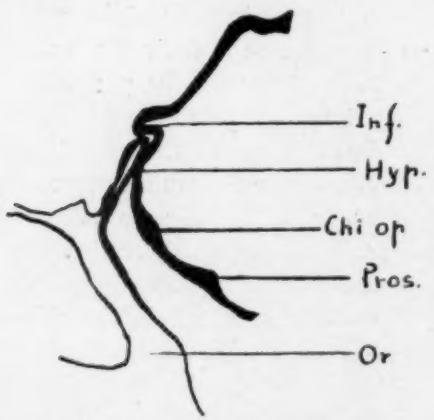

Fig. 1.—Origin of the hypophysis as a pharyngeal diverticulum: Inf., infundibulum; Hyp., hypophysis; Chi. op., optic chiasm; Pros., prosencephalon; Or., mouth.

Erdheim[7] in cross sections of normal glands found inclusions of pavement or ciliated cells near the superior and inferior portions of the hypophyseal cleft and within the gland, presumably representing "rests" of the primitive ectodermic diverticulum. He recorded seven heteroplastic tumors probably arising from such "rests."

Dean Lewis[8] emphasizes the frequency and importance of tumors arising from craniopharyngeal duct epithelium; reviews the literature with special attention to cases reported by Wagner, Langer and Har-

5. Mott, F. W., and Barrat, J. O. W.: Arch. of Neurol **1**:417, 1900.

6. Minot, C. S.: A Laboratory Textbook of Embryology, Philadelphia, P. Blakiston's Son & Co., 1910, p. 292.

7. Erdheim, J.: Ueber Hypophysengangsgeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissenschrift Math.-naturu. **150**: 1904; **113**:537.

8. Lewis, D. D.: A Contribution to the Subject of Tumors of the Hypophysis, J. A. M. A. **55**:1002 (Sept. 17) 1910.

bitz, and describes a case. He presents a table by Creutzfeldt, published in 1908, showing that in fifty-five necropsies of tumors of the hypophysis without acromegaly, nineteen were classed as craniopharyngeal duct tumors.

In the thirty cases of tumor of the third ventricle reported by Weisenburg,[9] only three are stated to be epidermoid in character. These include the cases of Saxer and Mott.

In the case here presented, the growth did not show the large polygonal cells with densely staining protoplasm, characteristic of tumors of the pars intermedia, nor did it resemble those arising from the choroid plexus. The infundibulum was distended, and its tissue

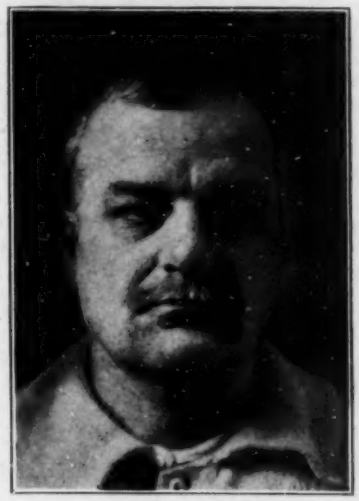

Fig. 2.—Patient, May 10, 1914.

partially replaced by the tumor with a suggestion of a tumor stalk near the right ventrolateral surface. Cross sections through the third ventricle and pituitary body, which was removed intact still attached to the brain, showed the dura-like capsule of the growth to be continuous with the connective tissue of the gland. The pituitary gland was normal. The squamous epithelium of the tumor showed a suggestion of intercellular spines and well marked scaling; but no hair or sebaceous material was found. Vacuolization and cilia formation are not differential, and there does not seem to be any adequate criterion by which one may judge how this epidermal tissue happened to be in this location. From the situation and character of the growth, it probably originated either as a result of a developmental abnormality of the infundibulum or from an hypophyseal "rest."

9. Weisenburg, T. H.: Tumors of the Third Ventricle with the Establishment of a Symptom Complex, Brain **33**:236, 1910.

In the grouping of third ventricle tumors according to symptomatology, suggested by Weisenburg[9] in an excellent review of thirty cases of which he reports three, this case would be in Class 1, i.e., those cases in which a tumor of moderate size is situated in the floor of the third ventricle and in which there is no extension into the foramen of Monro or the aqueduct of Sylvius. Though the aqueduct was not dilated, the posterior part of the ventricle and the peri-aqueductal structures were apparently involved indirectly as shown by the pupillary disturbance without, however, paralysis of associated ocular move-

Fig. 3.—Papillomatous character of the growth, type of epithelium and connective tissue stroma. Hematoxylin and eosin, × 70.

ments and a reeling gait suggestive of involvement of the red nuclei or superior cerebellar peduncles.

The patient's tendency to drag his feet and the weakness of the legs might be interpreted either as evidence of pressure on the internal capsules or of cortical injury.

One of the early symptoms in this case was the evidence of hypopituitarism (loss of sexual power, transient polydipsia and polyuria, and possible gain in weight). These may have been due to the fact that, occupying the base of the third ventricle, the growth at an early

date interfered with the discharge of a secretion of the posterior lobe of the pituitary gland directly into the cerebrospinal fluid, or to disturbance of function due to pressure on the whole gland. Histologically, no change was noted.

Another striking feature was the drowsy, somnolent, apathetic condition of over a year's duration, with periods approaching normality. Weisenburg does not consider this feature as specific of lesions of the third ventricle, but due to impairment of the normal function of the cortex, the result of pressure against the skull through dilatation of the

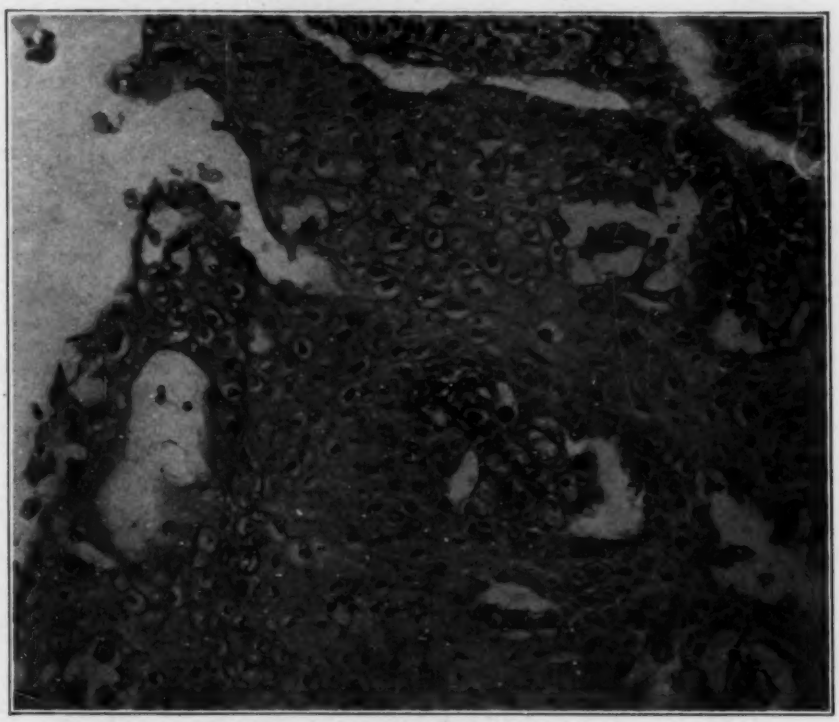

Fig. 4.—Inner aspect of cyst cavity. Hematoxylin and eosin, ×215.

lateral ventricles. Mott also believed it to be the result of compression of the cortex by internal hydrocephalus, and explained the recurrences by the escape of fluid from the lateral ventricles, thereby relieving the cerebral compression and removing the cerebral anemia. Purves Stewart[10] considered that somnolence in these cases was associated either with direct upward pressure on the third ventricle or with secondary anemia from compression of the vessels at the base of the brain.

10. Stewart, Purves: Four Cases of Tumor in the Region of the Hypophysis Cerebri, Rev. Neurol. & Psychiat., April, 1900, p. 239.

Turner [11] thought that it was due to cerebral edema. Cushing [12] notes hypersomnia in many cases of hypopituitarism and suggests, though certain cases showed sufficient increase in cerebral tension to possibly account for the drowsiness, that the condition may be associated with changes in glandular function. This relation has been considered as an explanation of normal sleep. The case reported by Purves Stewart in which a sarcoma (extracerebral) destroyed the pituitary gland without clinical evidence of somnolence, is in opposition to this theory.

Fig. 5.—Relation of the tumor to the thalamus. Cellular infiltration of the connective tissue. Hematoxylin and eosin, × 225.

In the case under consideration there was an internal hydrocephalus with increased intracranial pressure, cerebral anemia, edema and pituitary disturbance: it was not a suitable case for determining whether somnolence is a general diffuse effect, or results from the involvement of a focal center, possibly in the floor of the third ventricle or pituitary body.

The mental condition (change in disposition, enfeeblement of memory, disorientation, untidiness, etc.) is compatible with the fact

11. Turner, J.: Rev. Neurol. & Psychiat., June, 1910, p. 351.
12. Cushing: (Footnote 1) p. 269.

that the chief gross evidences of pressure were in the prefrontal areas. Sections from the second and third frontal gyri on the left showed loss of myelin in the fibers of the zonal layer. There was a slight diminution in the number of cortical cells, and those present showed considerable chromatolysis.

Areas Involved by Tumor.—The tumor directly involved by pressure the gray substance and fiber tracts about the third ventricle including:

Fig. 6.—Relation of base of growth to the pituitary gland. Globule of hyalin material. Hematoxylin and eosin, × 23.

(*a*) The anterior commissure containing fibers between the two hippocampal regions (pars temporalis), and those derived from the lobus olfactorius connecting the olfactory tract on the one side with the hippocampal region on the opposite side (pars olfactoria).

(*b*) The fornix composed of fibers arising in the hippocampal region, pursuing an arched course to the corpora mammillaria. Some fibers terminate here, others cross the midline and turn downward into the reticular formation as far as the pons.

(*c*) The lamina cinerea and lamina terminalis, a thin layer of gray substance between the corpus callosum and chiasma, continuous above

the chiasm with the tuber cinereum and connected at the side with the gray substance of the anterior perforated space.

(d) The optic chiasm and the optic tract, especially on the left, were distorted and flattened. The disks showed a marked papilledema and deposition of new tissue.

(*e*) The tuber cinereum — a lamina of gray substance extending forward from the corpora mammillaria to the optic commissure to which it is attached. It presents several small collections of ganglionic

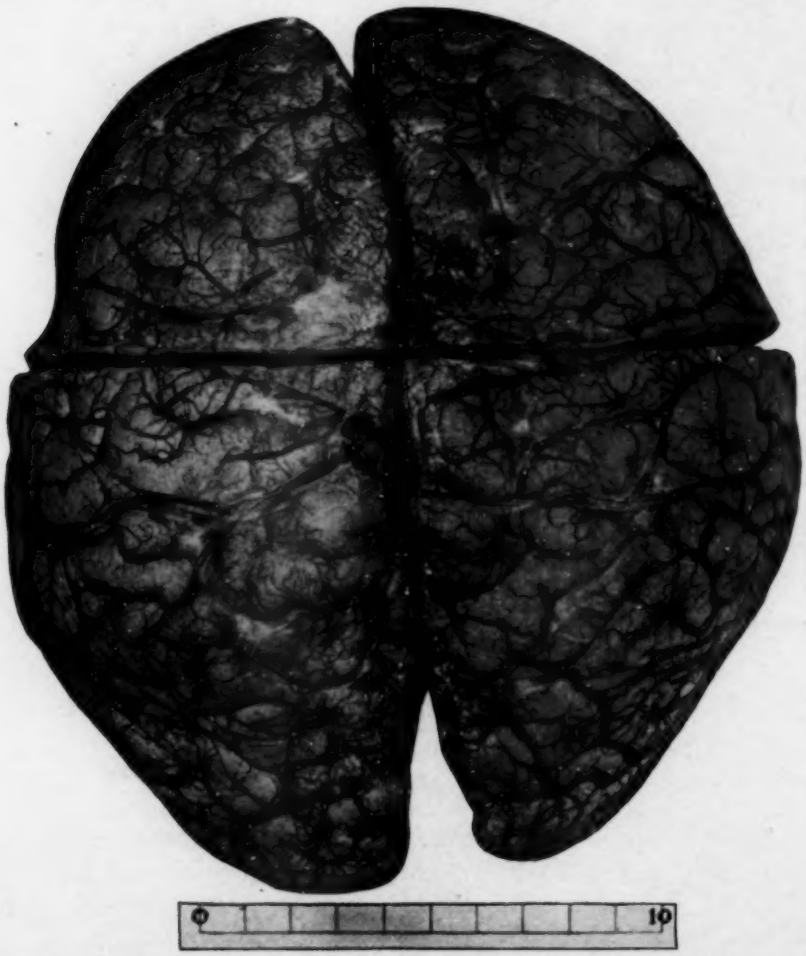

Plate A.—Upper surface of the brain. The brain before fixation tended to assume a round form when placed on a flat surface. The brain surface was dry, with a tracing of irregularly injected vessels. The convolutions were pressed out in appearance, the sulci being indicated on the right. The swelling of the brain and the widening and flattening of the gyri were most marked anterior to the posterior parietal lobules. The mesial surface also showed the flattening of the convolutions, especially on the left in the prefrontal region.

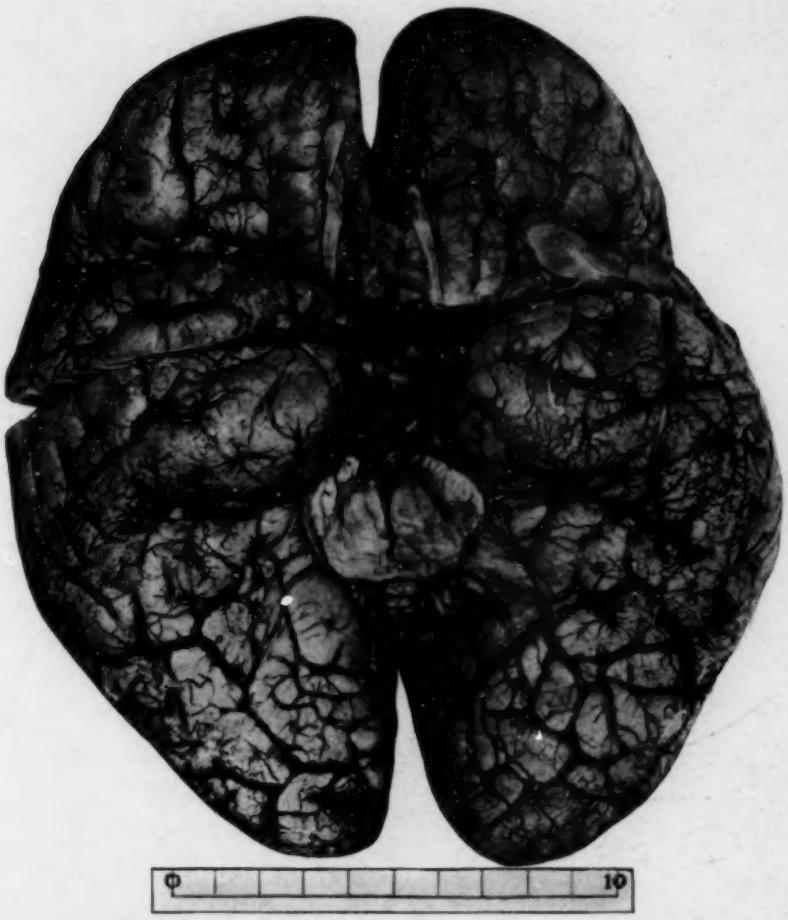

Plate B.—Lower surface of the brain. The vessels were small with inequality of the vertebrals. The left middle cerebral appeared small, and its lumen tiny. There was some hyalin change in the middle cerebral vessels, but no sclerosis. The olfactory bulbs were red and slightly unequal. The optic chiasm measured 2 by 1 cm.; it was much distorted as though from pressure beneath. The optic tract on the left was broad and bulging, the right less so. The optic nerves were flattened. The tuber cinereum was translucent gray. There was a small nodular protrusion of tissue on the right. The pituitary was normal in size and consistence. There were several grayish-yellow spots on the surface. The mammillary bodies were slightly flattened.

The pituitary gland, removed attached to the brain, appeared normal in size and outline.

The mammillary body on the left appeared swollen as though from pressure from beneath.

The third nerves were involved in a thickening of the pia between the peduncles. The brain stem in sections at the level of the red nuclei which appear as circular areas just dorsal to the substantia nigra and crusta.

The cerebellum appeared normal.

cells; the lateral eminences; the eminentia vascularis, homologue of the saccus vasculosus of lower vertebrates, especially prominent in the fishes. Johnston [13] considers the eminentia vascularis as possibly an organ for controlling the character of the spinal fluid. The basal optic ganglion (supraoptic nucleus Cajal)—a tract of gray matter with nerve cells, lying to the outer side of the tuber cinereum close to the optic tract. From each a tract issues, which, after decussating with that of the

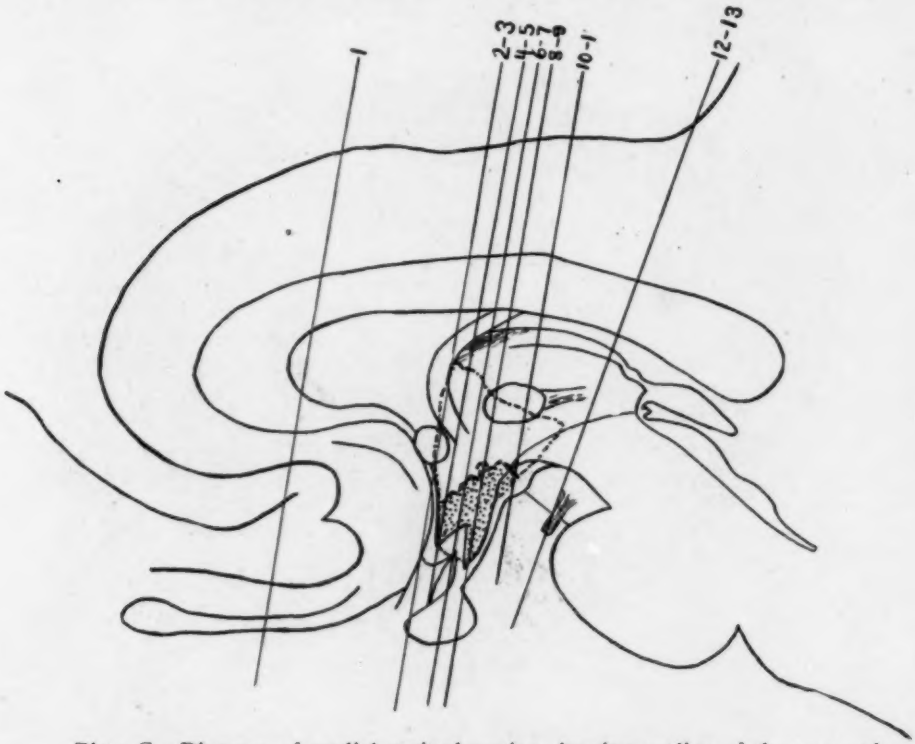

Plate C.—Diagram of medial sagittal section showing outline of the cyst and levels at which the following frontal sections were made.

In plates 3, 5, 7, 9, 11 and 13 one is looking toward the posterior pole of the brain.

In plates 2, 4, 6, 8, 10 and 12 one is looking toward the anterior pole of the brain.

opposite side (Meynert's commissure), applies itself to the mesial side of the optic tract and passes back to the lenticular nucleus. (Déjerine.)

(*f*) The corpora mammillaria, especially the mesial nuclei. Efferent tracts: Bundle of Vicq d'Azyr to the dorsal or anterior nucleus of the thalamus; bundle of Gudden to the red nucleus and adjacent gray matter of the tegmentum.

13. Johnston, J. B.: The Nervous System of Vertebrates, Philadelphia, P. Blakiston's Son & Co., 1906, p. 285.

Afferent tracts:[14] (*a*) by way of the columns of the fornix, and (*b*) through its peduncle from the main fillet and arcuate fibers in the tegmentum.

(*g*) Posterior thalamic decussation,[15] behind the mammillary bodies, probably a connection between the corpora Luysii. (Déjerine.)

(*h*) The intermediate gray mass or middle commissure, uniting the mesial nuclei of the thalamus across the third ventricle and continuous below on each side with the gray matter of the cavity.

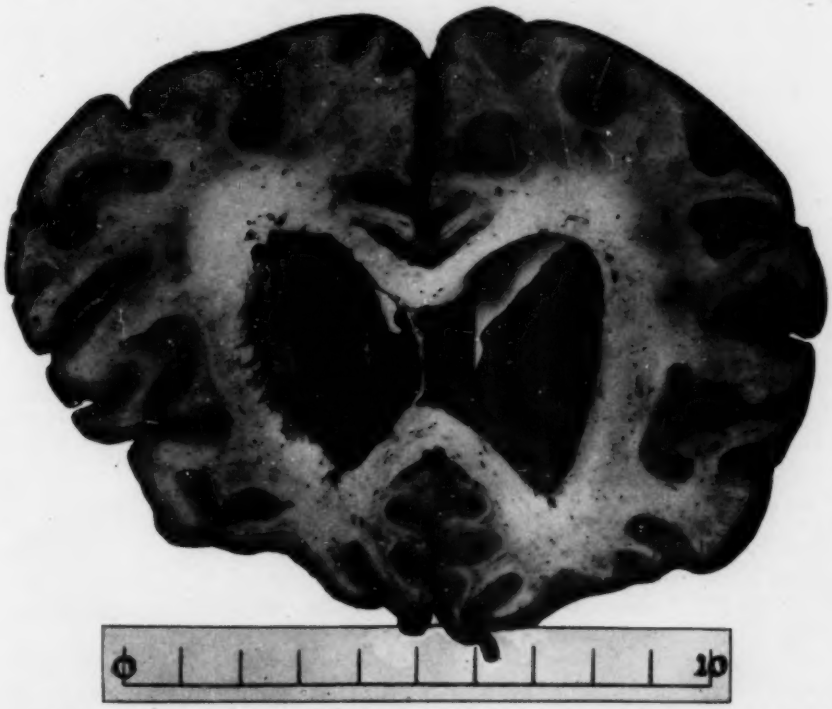

Plate 1.—Frontal section just posterior to the genu corporis callosis. Slightly oblique. The septum pellucidum extends between the truncus and rostrum corporis callosi. Lateral to the anterior horns of the ventricles is the stratum subependymale and on the right the corpus striatum before its division into the nucleus caudatus and the nucleus lenticularis by the traversing fiber bundles of the internal capsule. Converging toward the corpus striatum are seen the strands of the corona radiata. The olfactory bulb and tract are folded back beneath the section. The increased size of the left ventricle may be noted.

(*i*) The mesial series of nuclei of the thalamus (Cajal). There was no suggestion of a thalamic syndrome in this case.

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14. Quain, Jones, and Quain, Richard: Elements of Anatomy, Ed. 11, New York, Longmans, Green & Co. **3**:232, 1909, Part 1.

15. (Footnote 14) p. 228.

(*j*) Hypothalamus[16]—the prolongation of the tegmentum under the posterior part of the thalamus, divided by Forel into three layers from above down—the stratum dorsale, zona incerta and the corpus subthalamicum or nucleus of Luys, the latter having taken the place of the substantia nigra lying next to the prolongation of the crusta.

(*k*) The internal capsule. The possibility of determining capsular involvement was complicated by the cortical injury.

It has been difficult to estimate the degree of injury suffered by the tissues adjoining the growth, and even more difficult to correlate the injury with any clinical manifestations because of the diffuse area involved and the paucity of data as to the normal physiologic function of the structures.

CLINICAL DETAILS

The case was under the direction of Dr. Frankwood E. Williams.

History.—The history of the patient, a man, aged 52, white, was obtained from his wife. The family history was not important. He had been subject to headaches and vomiting in early life. At 33 he had typhoid fever. His application for life insurance had been rejected six years before because of albuminuria. He had pertussis in 1913. He denied venereal disease. He had lost sexual power one and one-half years before. He used no alcohol, and no drugs, but smoked a cigar occasionally.

The patient had been well until August, 1913, when he had occasional severe frontal headaches and complained of not feeling well. During the following months he had frequent headaches accompanied by constant nausea, but not by vomiting; he was abnormally sleepy and extremely irritable. In February, 1914, he drank large quantities of water, sometimes eighteen glasses in an hour; he again became lethargic and confused mentally, but was not considered seriously ill. He gave up his work. In April, he was frequently disoriented for time, his memory was poor, and his vision seemed to be failing. His speech became thick; he began to drag his feet, and he developed incontinence of urine.

He was admitted to the Psychopathic Department of Boston State Hospital, May 7, 1914. At first, he was excited, tore his blankets and sheets into strips and tied them in a fantastic manner about his feet. He was oriented for person, but not for place or time. There was a marked loss of memory for both recent and remote events with a tendency to fill the gaps with fabrications. He had some delusions of grandeur, magnifying the amount of his wealth and assuring the staff that he built all the buildings around the hospital. Definite evidence of hallucinations was not obtained. Emotionally, he ordinarily had been self-reliant, very cheerful, even-tempered, social (got on well with people), reserved but never seclusive. At the time of examination he appeared self-satisfied, somewhat euphoric and inclined to be restless. He had no insight into his condition.

Examination.—Physical: The patient was a well developed and well nourished man, 5 feet 8 inches in height, weighing 203 pounds, stripped. His face was flushed. The general examination was negative except for very slight edema over the feet and shins. The systolic blood pressure was 150 mm. of mercury.

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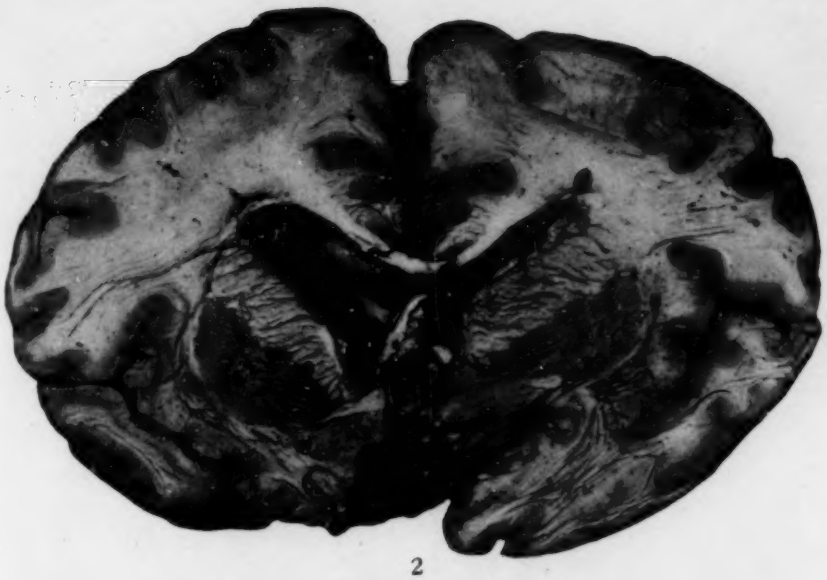
16. (Footnote 14) p. 250.



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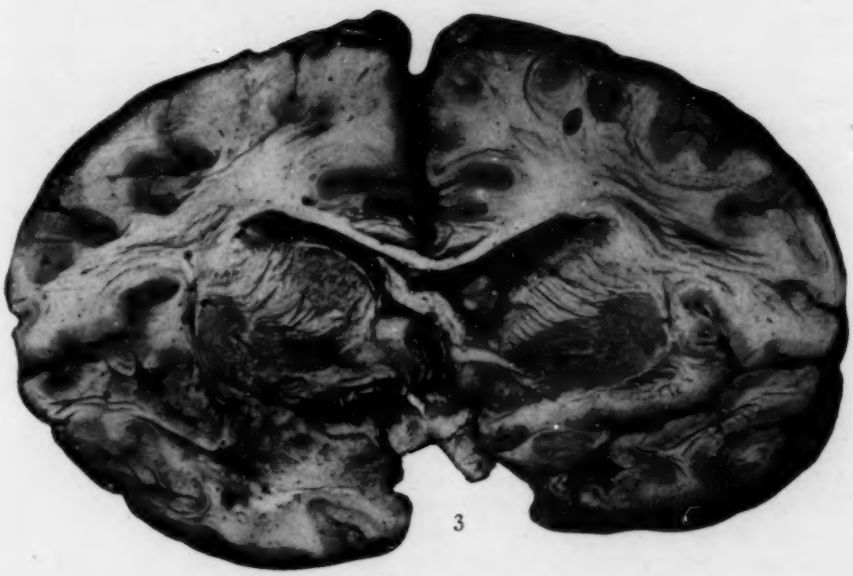

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Plates 2 and 3.—Oblique section. Left side shows more anterior level than the right. The internal capsule appears dividing the corpus striatum into the now small caudate, and the lenticular nuclei. The latter shows a subdivision into the globus pallidus and the putamen. On the right ventral to the corpus striatum lies the substantia perforata anterior, on the left the tuberculum olfactorium. The fibers of the anterior commissure are seen crossing the ventral part of the globus pallidus on the left, more laterally on the right. Ventral to the septum pellucidum appear the fiber bundles of the fornix, more prominent on the left.

Posterior to the recessus triangularis, rather loosely held to, but distorting, the columnae fornicis, anterior commissure and lamina terminalis is seen the sacular termination of the cyst occupying the base of the third ventricle. The foramen of Monroe is seen on the left. The increased size of both lateral ventricles may be noted.

Neurologic: The pupils were central, the right slightly larger than the left, and both were irregular. Consensual reaction and reaction to direct light were sluggish. Accommodation was normal. Extra-ocular movements were normal. There was no ptosis, strabismus or nystagmus. Examination was made of the fundi by Dr. Gerhardt in consultation, May 25, 1914. There was slight hyperemia of the disks, not pathologic. The deep reflexes were normal. Abdominal and cremasteric reflexes were not obtained. The gait and station were normal. There were no areas of anesthesia or hyperesthesia. There was no tenderness over the nerve trunks. Muscle sense was retained except for slight inaccuracy in the finger to nose test.

Laboratory Studies.—Urine: An occasional slight trace of albumin and a rare hyalin cast were found in the urine. A study of the acidity by the hydrogen-ion concentration method[17] gave evidence of a slight acidosis (plus 0.9, two hours after 4 gm. of bicarbonate of soda). The phthalein output was 18 per cent. The time was not stated.

Blood: The Wassermann reaction was negative. The cytologic examination was negative. Quantitative examination of uric acid, urea and nonprotein nitrogen showed a nitrogen retention (100 per cent. increase over the maximum normal values as given by Folin and Denis[18]).

Spinal Fluid: Three examinations were made. Cells, 2 to 6. Globulin was negative, and albumin was found in small amounts. The Wassermann reaction was negative. The colloidal gold test was negative for syphilis. There was 100 per cent. total nonprotein nitrogen increase. Urea at the pathologic threshold, based on normal values given by Mestrezat.[19]

Head: Roentgenographic examination of the head was negative, June 24, 1914.

Course of the Disease.—During the spring and summer, the patient remained confused, retarded and apathetic, took no care of his person, was untidy, and was frequently found lying about exposed. In October, because of the slight acidosis shown by the laboratory studies, he was given sodium bicarbonate by mouth. He became oriented for time, place and person; his memory improved, and he appeared to take more interest in current events. There were still periods when he was confused and when he had some difficulty in locomotion. At times he would walk like a drunken man. He had lost 39 pounds. Though not well, he was allowed to go home. In three weeks, he returned in a confused state, continually incontinent and very untidy. He remained in bed and refused to eat unless fed. There were a few short periods when he would brighten up and seem to know what was going on about him.

Jan. 3, 1915, after a febrile period of three days (white count 16,800), he became stuporous and died.

Summary.—The patient was a man of 52 years, who had been ill for sixteen months, and whose past history was negative except for typhoid fever nineteen years before and pertussis one year before the present history. There were loss of sexual power; rather acute onset of severe frontal headaches, with nausea but no vomiting; irritability and drowsiness, with increasing mental confusion; transient polydipsia; speech defect; difficult equilibration; distur-

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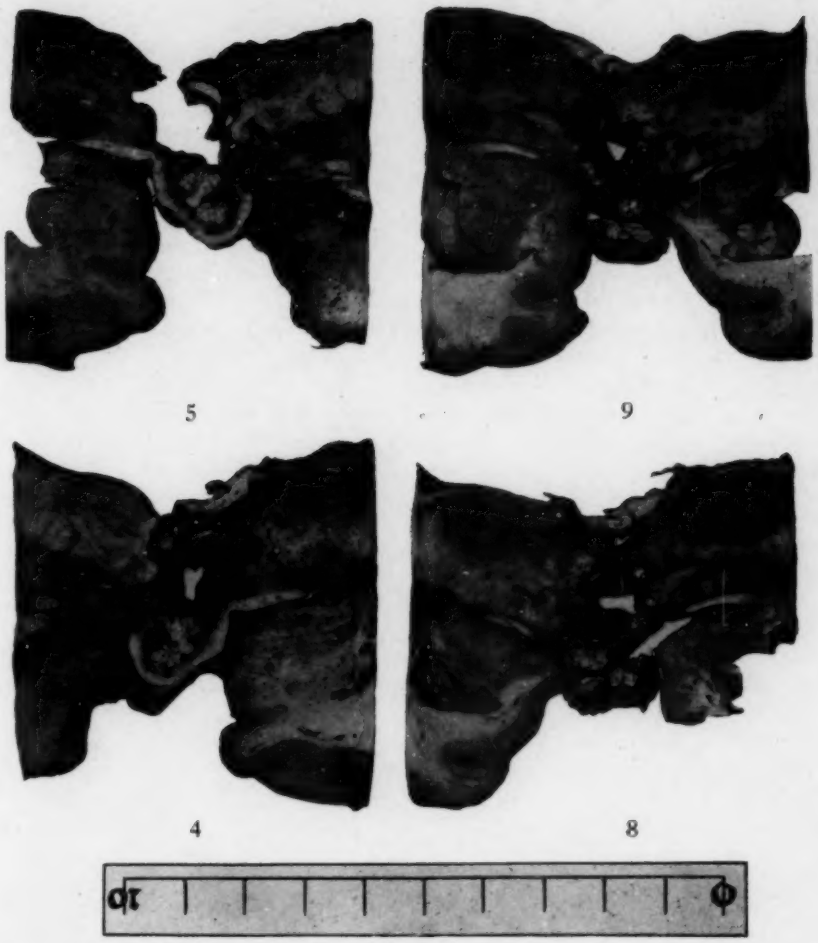
17. Palmer, W. W., and Henderson, L. J.: Clinical Studies on the Acid Base Equilibrium and the Nature of Acidosis, Arch. Int. Med. **12**:162 (Aug.) 1913.

18. Folin, O., and Denis, W.: Protein Metabolism from the Standpoint of Blood and Tissue Analysis, J. Biol. Chem. **14**:29 (Feb.) 1913.

19. Mestrezat, W.: Le Liquide Cephalo-Rachidien, Paris, 1912, pp. 108, 249.



Plates 4 and 5.—On the left the section strikes through the anterior end of the thalamus. The columnae fornicis lie lower on both sides while the crurae assume a dorsal position. Their attachment to the corpus callosum has been torn. On the right, the thalamus exhibits differentiation into the nucleus anterior, and the nucleus lateralis and the nucleus amygdalae appear within the temporal lobe. The third ventricle is increased in size, irregular in outline and almost completely replaced by the cyst. There is a free upper surface which lies folded on itself across the distended upper portion of the ventricle. The grayish limiting wall can be traced in apposition with the remaining structures about the ventricle. The basal portion of the cyst contains a whitish cauliflower-like growth displacing the fibers of the optic chiasm, more markedly on the left, and causing the rounded swelling of the left optic tract noted in the description of the base of the brain. Around that portion of the growth, extending into the pocket in the optic tract, is a semicircular mass of colloid material.

Plates 8 and 9.—Section passes through the anterior end of the massa intermedia which is flattened by the distention of the third ventricle and pressure of the cyst which protrudes into it from below involving chiefly the mesial nucleus of the thalamus and bundle of Vicq d'Azyr on the right. There is a small pocket between the cyst wall and the overlying commissure on the left. The portion of the third ventricle above the massa intermedia is flattened but patent. The infundibulum is filled with the growth which bulges into the left side. The pituitary in section shows grayish areas. Microscopic preparations were made from this section.

bance of vision; disorientation; memory defect with tendency to fabrication; expansive delusions; restlessness; untidiness, with a lack of appreciation and indifference to his condition.

Physical Signs: The right pupil was larger than the left. Both were irregular and reacted sluggishly to light. There was a slight speech defect. There were tremor of the extended fingers, increasing weakness of the legs, a tendency to drag the feet, and a loss of control of both the rectal and vesical sphincters.

Laboratory Findings: All tests for syphilis were negative. A slight trace of albumin and casts was found in the urine. There was low kidney function. The blood pressure was 150 systolic. There was retention of nitrogenous products in the blood and spinal fluid, and an increased white count shortly before death.

The case was presented at a meeting of the staff of the Psychopathic Department, May 16, 1914. It created considerable interest and discussion; but no consensus of opinion was reached. It was noted that the case clinically resembled general paralysis; but such diagnosis would hardly be ventured with all tests for syphilis negative. The picture in some respects simulated the terminal stage of Korsakoff's syndrome, but presented no etiologic factor, as alcohol or other toxic agent. No definite indication or localizing sign of arteriosclerosis was present. The evidence of chronic infection, pyogenic or tubercular, was not convincing. Brain tumor was considered; but there were negative eyegrounds, and no localizing signs; an intracranial growth was considered improbable. Although the findings were not typical of uremia, because of the low kidney function, retention of nitrogenous products in the blood and spinal fluid and urinary findings, the case was classified as a cardiorenal psychosis.

Necropsy.—Two hours after death, necropsy was performed by Drs. Solomon, Bunker and Bloomer.

A summary of the positive findings with reference to the body is noted in the anatomic diagnosis.

Kidneys: They weighed 240 gm. They measured 11 by 5 by 2.5 cm. Five small cysts dotted the surface. The capsules were slightly adherent, and the pyramids were poorly differentiated.

Thyroid: It was firm, and section showed nothing of note.

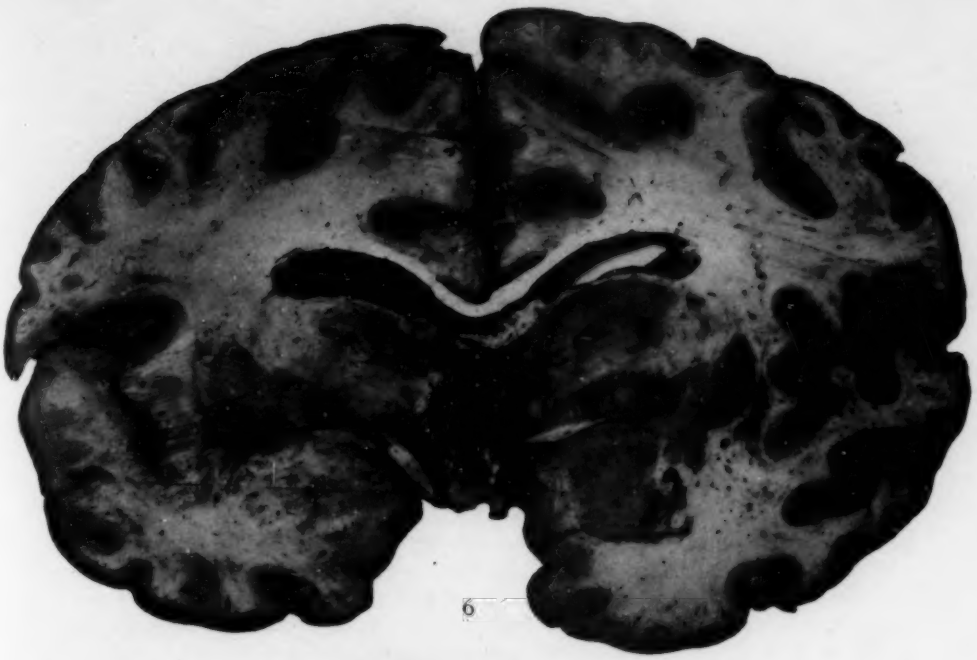
Suprarenals: They were very small, the cortex measured 0.1 by 0.2 cm. in thickness. Two lines of the cortex approximated in one limb; the second limb was separated by a brownish medulla which showed a slight hyalin change in one suprarenal.

Pancreas: It was normal.

Testes: Threaded well.

Head: Description of the brain is given by Dr. Canavan. The hair was somewhat scant. The periosteum was negative. Calvarium measurements were: frontal, 1 cm.; temporal, 0.4 cm., and occipital 0.7 cm. Depressions for the pacchionian bodies were slightly to the right of the median line and pierced the inner table at the vertex. Grooving for the middle meningeals was shallow on both sides.

The dura was not adherent, but was tense; and the brain filled the dura completely. Convolutions were seen through the dura. There was no subdural fluid; and on peeling back the dura mater, the pia appeared not to be present, only a tracing of irregularly injected vessels pressed on a smooth brain surface. The pial surface of the brain was dry.



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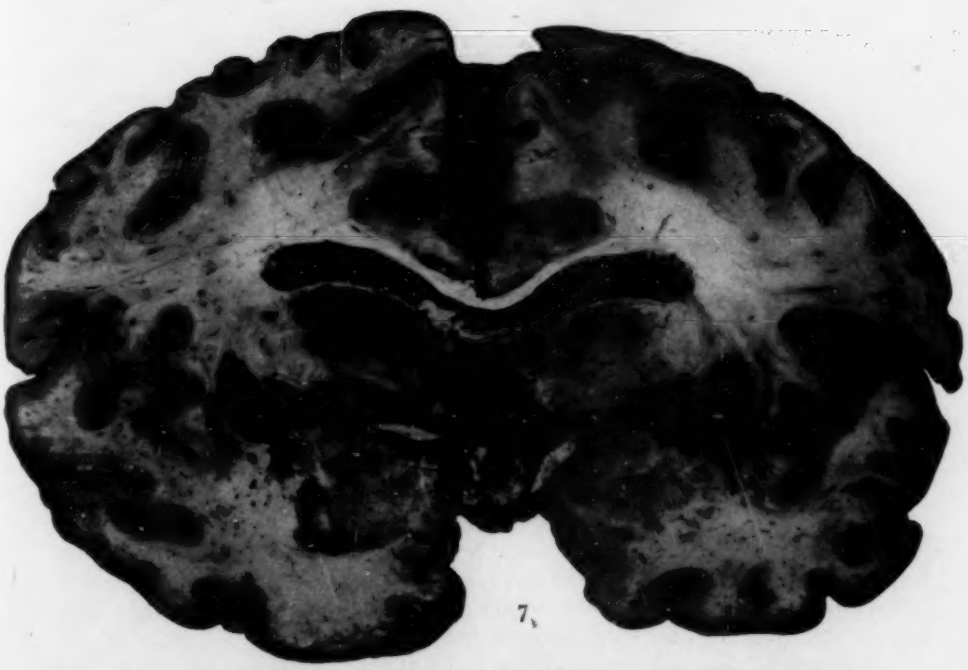

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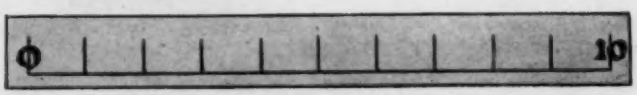


Plates 6 and 7.—The distention of the third ventricle is more marked; the tumor mass at the base of the cyst now filling the tuber cinereum is larger, and there is a small knob-like extension of the growth on the right. There is marked distortion of the optic tracts. The columnae fornicis lie deeper. The relation to the thalami, and on the right, approximation to the internal capsule which now penetrates farther baseward and is traversed ventrally by the fiber strands from the nucleus lenticularis assembling to form the fasciculus lenticularis (Forel) may be noted. Microscopic preparations were made from the anterior portion of this section.

The superior surface of the brain tended to assume a round form when placed on a flat surface. The hemispheres strained from each other. At the frontal poles, particularly on the left, the convolutions were smooth and pressed out in appearance. The sulci were indicated on the right. The swelling of the brain and the widening and flattening of the gyri were most marked anterior to the posterior lobules. Even the mesial surface showed the flattening of convolutions, especially on the left in the prefrontal region.

At the base of the brain, the vessels were small, the vertebral arteries were unequal, the left being larger than the right. There was some hyalin change in the middle cerebrals, but no sclerosis. The middle cerebral artery on the left appeared very small, and its lumen tiny.

The olfactory bulbs were red and slightly unequal; but the tracts were white. There was a sharp differentiation between the bulbs and the tracts.

The optic chiasm was flattened from pressure beneath, especially on the left side, and the form of the optic nerves was much distorted. The optic chiasm measured a little more than 2 cm. from side to side and spread for a distance of nearly 1 cm. on the left. The tract which leaves the chiasm for the geniculate bodies on the left was broad and thin in appearance from pressure of a swelling from beneath. The distal ends of the optic nerves appeared infringed on and did not assume their round contour, but were irregularly wishbone in shape. The space between the chiasm and the mammillary bodies was translucent gray, it measured 3 by 3 cm., and a puncture of it for securing fluid from the third ventricle showed a thick, purulent, pinkish semifluid substance, a smear from which by Gram's stain, showed many large mononuclear cells with large nuclei; some polymorphonuclears that looked remarkably small in comparison. There were no organisms. When stained by Wright's stain they showed polymorphonuclears (small), red blood cells, and large endothelial and transition lymphocytes. The lobus pyriformis on either side was flattened and thin. The pons measured 4 by 3 cm. and the medulla 2 by 2 cm. The third nerves were involved in a thickening of the pia which forms a part of the floor of the third ventricle.

The optic nerves in their orbital portion showed nothing of note.

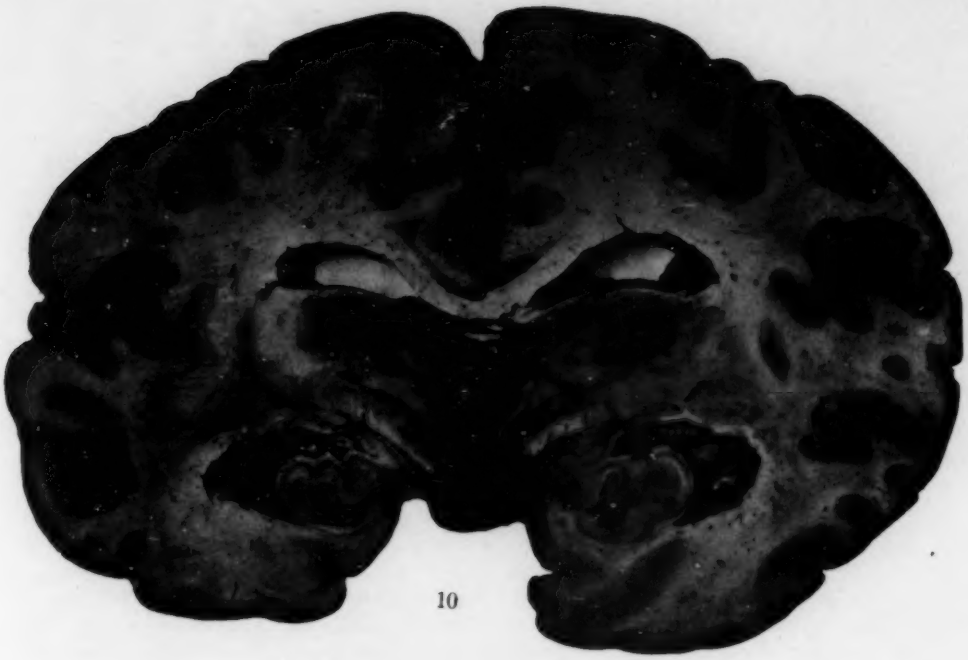
The middle ears, Gasserian ganglions and pituitary gland were negative.

The brain's weight was 1,575 gm. Tigges' formula 8 by 172: 1,376 gm. The gain in brain weight was 199 gm.

The cord was firm and showed nothing of note.

A frontal section revealed a marked difference in size in the anterior section of the lateral ventricles, the right measuring 4 by 3.5 cm. at the wider end, and 1.5 cm. at the inferior portion. The left ventricle cut at the same plane measured 5.3 by 4.2 cm. at the upper, and 1.5 cm. at the inferior. On cross section of the third ventricle, the tissues were found to be soft and edematous, and the capacity of the third ventricle markedly increased.

Anatomic Diagnosis.—The man was well nourished. There were, injection of appendix; sclerosis of the coronaries and aorta; chronic fibrous endocarditis, tricuspid; chronic fibrous endocarditis, mitral; chronic fibrous endocarditis, aortic; fenestration of the aortic valve; apex—scar; pulmonary congestion; chronic interstitial nephritis; chronic perihepatitis; a cyst in the liver. The calvarium was thick; the pia dry; the brain was swollen and smooth. Chronic internal hydrocephalus. Chronic cerebral abscess of the third ventricle and hyaline basal vessels were present. The brain weighed 1,576 gm., the gain in brain weight being 199 gm.



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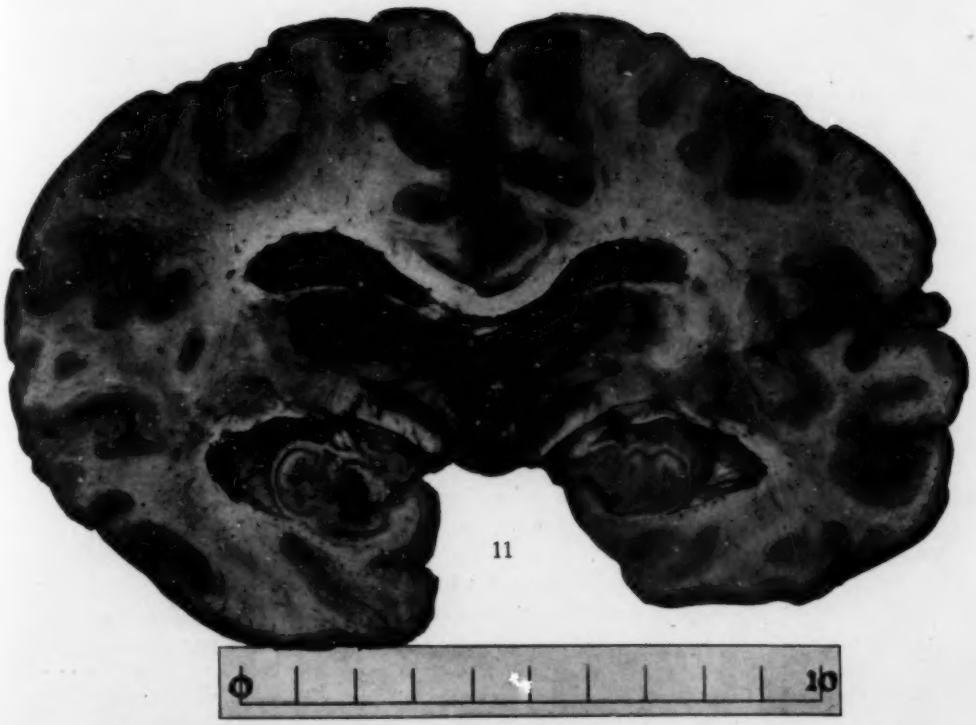

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Plates 10 and 11.—Section passes obliquely through the posterior portion of the massa intermedia and the mammillary bodies. Separating the latter and completely occupying the lower portion of the third ventricle, the cyst is triangular in shape, and there is no growth in the basal portion at this level. The terminal fibers of the fornix are seen entering the lateral nucleus of the mammillary body, and the bundle of Vicq d'Azyr ascending from the mesial nucleus toward the anterior nucleus of the thalamus. Weigert's specimen from the anterior portion of this section shows no loss of myelin in the surrounding structures.

Microscopic Findings.—The visceral organs were fixed in Zenker's solution, embedded in paraffin and stained by eosin and methylene blue and Mallory's connective tissue stain.

Kidneys: There was focal infiltration of the interstitial tissue of the cortex by cells of the lymphocytic series. There was a rare sclerosed glomerulus, compatible with a slight degree of chronic vascular nephritis. They were essentially normal kidneys for a man of 52.

Pituitary: There was normal glandular structure.

Testes: The spermatogenous epithelium showed development of spermatocytes and occasional spermatids, but no mature spermatoza. There was a decrease in the interstitial cells.

Thyroid, suprarenal and pancreas showed no pathologic change.

Spleen: The capsule was thickened. A large amount of intracellular dark brown pigment was present. There was an increase in the connective tissue of the end arteries. Malpighian bodies showed some edema and focal destruction of cells with amyloid deposits.

Liver: Formaldehyd fixation followed by sudan III showed increase of fat in small droplets, chiefly around the portal vessels.

Other organs showed increase in connective tissue around vessel walls. There were a large number of eosinophils in the lymphoid tissue of the large intestine.

The brain and other nervous tissues were fixed in liquor formaldehydi embedded in celloidin, and stained by the methods of Weigert and Marchi, and with cresyl-violet for cell studies.

Longitudinal sections through the heads of the optic nerves showed the disks to be twice the normal thickness, with retention of a definite cupping but deposition of new tissue. There was slight cellular infiltration along the more minute vessels. The retina showed low folds near the disks. There were distention of the vessels within the optic nerves and marked dilatation of the intervaginal spaces with the arachnoid prominent. Cross section of the left nerve showed a small triangular area with loss of myelin.

Peripheral Nerves: They were negative.

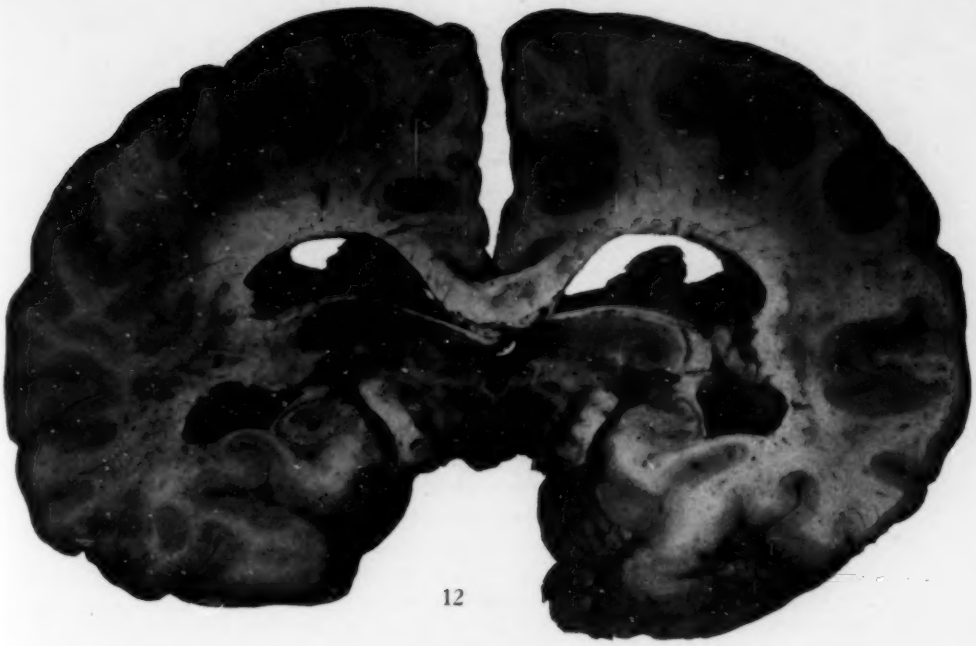
Sympathetic Ganglions: The nuclei were centrally placed. There was peripheral arrangement of the Nissl substance and abundant pigment.

Gasserian Ganglion: The cells were large, and the nuclei were centrally placed. The Nissl substance was finely granular, and evenly distributed through the cells. Few cells showed pigment. The cells were shrunken from the nucleated sheaths.

Cord: Sections from the cervical, thoracic and lumbar regions showed no loss of myelin. A few of the anterior horn cells at each level were filled with fat in very fine droplets.

Sections of the tumor were stained with cresyl-violet, hematoxylin and eosin, Mallory's phosphotungstic acid hematoxylin, Verhoeff's elastica and Van Gieson.

The cyst appears encapsulated by a supporting layer of vascular connective tissue on which is a stratified epithelium, varying in thickness from a few to many cells with extensive desquamation of the superficial layers. There is a tendency to the formation of prickle cells, but no epithelial fibrils or "pearls." Mitotic figures are not numerous. Though the contour of the infundibulum is essentially retained, its tissue is largely distorted by the growth which fills the cavity and which, in this region, appears as a papillary cauliflower-like mass. On the right ventrolateral aspect, there is more abundant vascular connective



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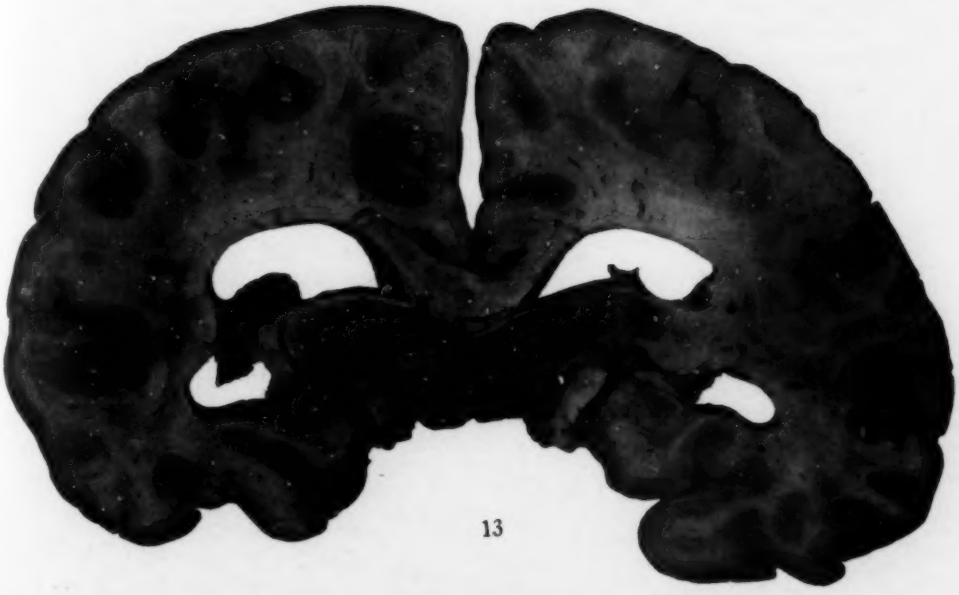

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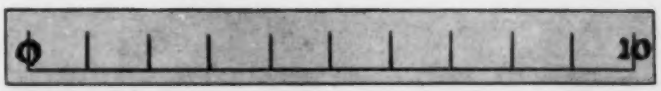

Plates 12 and 13.—Oblique section behind the massa intermedia and passing through the red nuclei. The posterior portion of the cyst wall is seen in the third ventricle lying below the massa intermedia just anterior to the red nuclei. There is dilatation and flattening of the third ventricle above the massa intermedia. Sections at this level stained by Weigert and Weigert-Pal show no lesion.

tissue with radiations into the papillae suggesting a tumor stalk. There are several finger-like projections and a small cystic protrusion latterly from this area. In the center of the basal proliferation, there are a few narrow spaces surrounded by a single layer of large deeply staining columnar vacuolated cells resembling goblet cells, and occasionally a few columnar cells with a suggestion of cilia formation. No hair or sebaceous material was found. The stroma is relatively small in amount, contains numerous blood vessels and in some places is infiltrated with polymorphonuclear leukocytes. There are a number of finger-like projections from the tumor but no definite break in the connective tissue capsule was found. The capsule resembles dura in structure and is continuous with the connective tissue about the pituitary gland which was removed intact with the brain. There are a few hyalin globules just below the growth between it and the gland.

There is some gliosis of the surrounding brain tissue, and there is evidence of retrograde metamorphoses. There are numerous collections of polymorphonuclears and endothelial cells containing fat and pigment. Some areas seem to have undergone a hyalin degeneration.

There are none of the large polygonal cells with densely staining protoplasm characteristic of tumors originating from the cells of the pars intermedia. The growth has not the extensive vascularity or angiomatous character frequently seen with plexus tumors.

Sections from the second and third left frontal convolutions were stained with Weigert, Marchi and cresyl-violet. There is a loss of myelin in the fibers of the zonal layer as compared with Campbell's charts. The cortical cells are slightly decreased in number. The remaining cells appear edematous. Frequent cells show eccentric, poorly staining nuclei and diminution in the Nissl substance. This is more marked in the larger cells. Marchi preparations show an increased fat content in a few of the ganglion cells. There is no phagocytosis.

SUMMARY

In this case presenting an epidermoid papillary cystoma involving third ventricle, the tumor probably originated either from a hypophyseal "rest," or as a result of a developmental abnormality of the infundibulum. The clinical signs and symptoms of sixteen months' duration did not lead to a localization before death. Correlation of clinical and pathologic findings has been complicated by the difficulty of separating local from remote and general effects, and the paucity of data as to the normal physiologic function of the structures involved.

It gives me great pleasure to acknowledge my indebtedness to Dr. E. E. Southard for creating the atmosphere that made this study possible and for constant stimulating and helpful suggestions.

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20. In addition to the references already given, the following will be found of interest:

Farnell, F. J.: An Extra Cerebral Tumor in the Region of the Hypophysis, New York M. J. **40**:462, 1911.

Pollock, L. J.: Tumor of the Third Ventricle, J. A. M. A. **64**:1903 (June 5) 1915.

BRAIN TUMORS AS SEEN IN HOSPITALS FOR THE INSANE*

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BOSTON

It is not a rare experience for the pathologist in a hospital for the insane to find at necropsy a brain tumor undiagnosed during life. The objects of this paper are to inquire into the reasons for the lack of diagnosis, and to find out whether the group of brain tumor cases in hospitals for the insane presents any special characteristics as to symptomatology, age or stage of disease on admission, which would distinguish them from cases in general hospitals.

All brain tumor cases coming to necropsy during the past ten years in the Boston, Danvers, Taunton, Westboro and Worcester State Hospitals and the Psychopathic Hospital were studied, as were also single cases at the Medfield, Foxboro, Bridgewater and Northampton State Hospitals. Gummas were excluded. The histories and necropsy protocols of forty-six cases thus collected were studied, and in most instances the brains were examined in frontal sections. In about half of the cases the brains and cords were also studied histologically.

The percentage of brain tumors as compared to the total number of necropsies agrees fairly closely in the different institutions: Boston State Hospital, 1.9; Danvers State Hospital, 1.3, and Westboro State Hospital, 2.6. These percentages are about the same as that found by Cushing[1] in the Johns Hopkins Hospital necropsy records up to January, 109, namely, 1.7 per cent.

The age incidence of patients with brain tumors in the state hospital groups presents an interesting and significant deviation from that of such patients in general. The distribution by decades is: from 11 to 20 years, one; from 21 to 30, three; from 31 to 40, four; from 41 to 50, eighteen; from 51 to 60, thirteen; from 61 to 70, five; from 71 to 80, one; from 81 to 90, one.

The average age is 50 years. Bruns[2] states that brain tumors are most frequent from puberty to 30 years, then from 30 to 40 years; more than half of his cases occurred between the twentieth and fortieth

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*From the Laboratory of the Boston State Hospital. Contribution in a series offered to Prof. E. E. Southard in honor of the decennium of the Bullard Professorship of Neuropathology, Harvard Medical School.

1. Cushing: In Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger **5**:308, 1915.

2. Bruns: Die Geschwulste des Nerven-Systems, 1907, p. 61.

years. He, however, includes tubercles and gummas, so that the two series are not strictly comparable. In Cushing's series of 130 cases the maximum number occurred between the twentieth and fortieth years. It appears, however, that the average age of patients with brain tumor sent to hospitals for the insane is greater than that of brain tumor patients in general.

The sites of the tumors, in order of frequency were: frontal, fifteen; temporal, six; multiple (metastatic), pituitary and intraventricular, four each; cerebellar or cerebellopontile, five; central fields, parietal and corpus callosum, two each; occipital and peduncular, one each. The large proportion of frontal tumors (33 per cent.) is significant, as in the statistics of Schuster[3] for brain tumors in general, cerebellar growths lead with a percentage of 21.6; followed by multiple, 14.7 per cent.; frontal, 12.1 per cent., and central, 12 per cent.

TABLE 1.—Sources of Group of Patients with Brain Tumor Sent to Hospitals for the Insane

Sent by private physicians (undiagnosed)	31
Sent from general hospitals (undiagnosed)	6
Sent from general and special hospitals (diagnosed)	2
Sent from general hospitals after operation for brain tumor	2
Developed in patients in hospitals for the insane	4
Voluntary admission	1
	46

TABLE 2.—Stage of Disease at Which Patients Were Admitted

Early, that is, soon after the appearance of the symptoms*	4
Advanced, the symptoms dating back from one and a half to three years, and the patients living from one to four years after commitment	8
Greatly advanced, the patients surviving only a few months after admission	19
Terminal	11

*One patient was sent to an institution for epileptics and later to a hospital for the insane.

TABLE 3.—Symptoms Necessitating Commitment

Simple deterioration (neurologic signs also present)	10
Convulsions, with or without mental deterioration	4
Confusion, hallucinations and disturbances of memory, the latter appearing as transitory amnesia, a general reduction of immediate and remote memory, or an almost total loss of immediate retention	9
Lethargy and somnolence	8
symptoms of psychosis (manic-depressive, dementia praecox and senile dementia) antedating symptoms of tumor, but the latter present at time of admission	5
Aphasic and apraxic disturbances	3
Predominantly physical disabilities (blindness and deafness) with irritability and mild paranoid trend	2
Confusion and physical weakness	1

3. Schuster: Psychische Störungen bei Hirn Tumoren, 1902, p. 298.

The diagnoses made after the patients reached the hospitals for the insane revealed the small percentage of cases in which the correct diagnosis was made and the conditions with which brain tumor was confused. The diagnoses were: brain tumor, fifteen; "organic dementia," eight; cerebral arteriosclerosis, four; epilepsy and paresis, three each; cerebellar disease, two; cerebral hemorrhage, Korsakoff's psychosis, manic depressive and dementia praecox, one each; unclassified, two; senile dementia, two.

MISTAKES IN DIAGNOSIS

The diagnosis of brain tumor was made in only one third of the cases (including four admitted from other hospitals with the correct dagnosis). The cases diagnosed as paresis would probably be correctly diagnosed at the present time with the routine examinations of the spinal fluid now general in hospitals for the insane. Tumors in senile persons are difficult to diagnose. Mistakes in diagnosis tend to fall into three groups: deteriorated cases with neurologic signs are called paresis, Korsakoff's psychosis or put into the catch-all of "organic dementia"; cases presenting focal signs are confused with arteriosclerosis, and those with convulsions are merely called epilepsy.

A surprisingly small proportion of cases of brain tumor are diagnosed correctly. There are several reasons: First, the training and point of view of the physician in a hospital for the insane is psychiatric rather than neurologic, and he is preoccupied with the mental symptoms. In general hospitals, of course, the reverse tendency prevails. Second, the most fundamental reason is that, as a rule, ophthalmoscopic examinations of patients presenting organic signs are not made unless brain tumor is definitely suspected. If such examinations were made, a much larger percentage of tumors would be diagnosed, and until they are made as a routine measure, the percentage of cases of brain tumor diagnosed will not be much raised. It would appear that there is no more reason for neglecting this diagnostic aid in any organic case than for omitting a Wassermann test. Third, the use of the term "organic dementia" as a sufficient designation discourages any refinement of diagnosis. Fourth, the group of tumor cases seen at state hospitals offers peculiar liability to confusion in diagnosis. A large proportion of the cases occur in middle age when deteriorating psychoses, such as paresis, Korsakoff's psychosis and cerebral arteriosclerosis are common, and are naturally first considered. This is particularly true of cerebral arteriosclerosis which frequently coexists with brain tumor; when it occurs, the exclusive diagnosis of arteriosclerosis is apt to be made to cover all symptoms.

A study of the frequency of arteriosclerosis was made in all the available brains of this series. In eighteen of thirty-nine there was notable arteriosclerosis, both of the basal and of the small cortical vessels — all in persons in the fifth decade or beyond. In eight the degree of arteriosclerosis was advanced, and in three small cysts of softening were present.

A microscopic study of the brain was made in nineteen cases. The changes in regions not immediately affected by the tumor were not uniform, nor were they striking, aside from the cases in which arteriosclerosis was present. Lamination was well preserved, but the cells were sometimes askew in arrangement. Chromatolysis was occasionally present, as was an increase of satellites and perivascular pigment. Gliosis, particularly subpial, was frequent, in both the arteriosclerotic and nonarteriosclerotic cases.

Certain tumor groups are of particular psychiatric interest, namely, the frontal, temporal, parietal, ventricular and callosal. These will be considered in detail elsewhere, and only a few points touched on here.

FRONTAL TUMORS

It is difficult to get a clear-cut clinical picture of this group. All of the patients except two (an alcoholic dement and a senile patient) were admitted in the late or terminal stage, and the most prominent feature at the time of entrance was deterioration, usually accompanied by apathy, sometimes however by confusion and excitement, and frequently by somnolence. Deterioration was the most pronounced and constant characteristic. The special importance of frontal tumors for the production of dementia is generally assumed, but has been questioned by von Monakow,[4] Müller[5] and Bruns, among others, their view being that frontal growths usually attain a large size before encroaching on vital centers, and that the psychic changes attributed to the specific involvement of the frontal areas are in reality due to diffuse injury of the cortex, increase in intracranial pressure and interference with circulation. This series is not adapted to throwing light on the question because of the advanced stage at which the patients came under observation, and because of the lack, in most cases, of a full history of the early part of the illness. Nor was it possible always to differentiate between "Benommenheit" and true dementia, although the descriptions in most instances leave no doubt that there was real mental reduction.

4. Von Monakow: Lokalisation im Grosshirn, 1904.

5. Müller, E.: Deutsch. Ztschr. f. Nervenh. **23**:378, 1902-1903; **21**:178, 1901-1902.

Müller,[5] in his analysis of 164 cases of frontal tumor, finds that a larger proportion occur in middle life (from 40 to 60 years) than is the case with tumors of other regions. The maximum of his curve is at from 31 to 40 years, 26 per cent., followed by 20 per cent. at from 41 to 50 years and 16 per cent. at from 51 to 60 years. The distribution of the state hospital series is: from 11 to 20 years, one; from 21 to 30, none; from 31 to 40, two; from 41 to 50, six; from 51 to 60, three; from 61 to 70, two; from 71 to 80, none; from 81 to 90, one.

The average age is 50½ years. There are no significant differences between the average ages of patients with frontal tumors and those with tumors of other areas (posterior fossa, 45½ years; all regions except frontal, 48 years). but it is interesting to note that the average age for all classes of tumors is above that given by Müller.

Epileptic convulsions were present over a considerable period in three patients, frontal ataxia in three (causing the diagnosis of cerebellar disease), and in two patients there was early the somnolence supposed to be particularly characteristic of frontal growths.

The large percentage of frontal tumors in the state hospital series may be due, not to any peculiar relation between frontal growths and dementia, but to the fact that disturbances from these tumors are, in many cases, not obvious, unless the patients are under close observation (as they usually are not) until a late stage, when the final deterioration necessitates commitment. Also, in the absence of striking neurologic signs, the psychic symptoms stand in the foreground, and the patient is sent to a hospital for the insane rather than to a general hospital. Another factor, that of an increasing tendency to deterioration with advancing age, will be discussed later.

TUMORS OF TEMPORAL LOBES

Tumors of the temporal lobes are of special interest on account of uncertainty of the diagnostic features of tumors in these regions. Cushing states that, with the exception of the uncinate area, the temporal lobe is a relatively silent region, even on the left. Several authors have tried to differentiate a syndrome common to tumors of both sides. Foster Kennedy[6] emphasizes the epileptic convulsions and their equivalents of dreamy states; crude, subjective sensations of smell and taste, with or without involuntary movements of mastication; and after the attacks, transient weakness of the contralateral lower facial muscles, less often of the arm and leg, and increase of the deep reflexes. The motor symptoms and reflex changes later become persistent.

6. Kennedy, F.: The Symptomatology of Temporosphenoidal Tumors, Arch. Int. Med. **8**:317, 1911.

Albert Knapp[7] gives as a syndrome characteristic of both lobes, homolateral ptosis and mydriasis, contralateral hemiplegia and cerebellar ataxia. Bruns and Aswazoturow[8] consider that periods of auditory hallucinosis may be the equivalent of the convulsions. Mingazzini[9] divides the temporal lobe into four zones, the tumors of each having a characteristic symptomatology. Zone 1 consists of the anterior portion of the convex surface, and its syndrome is total hemiparesis, associated with contralateral ptosis and paresis of one or both abducens. Zone 2 comprises the posterior half of the convex surface. In tumors of this region hemiparesis is almost constant, and all branches of the oculomotor may be affected; also, there is a tendency to conjugate deviation of head and eyes and ataxia of the cerebellar type. If the tumor is on the left, sensory aphasia or dysarthria are present with tumors of both zones. In the third zone, the posterior part of the inferior surface, the most frequent signs are unilateral paralysis of the abducens, isolated paralysis of the facial, contralateral ptosis, hemiparesis and hemianesthesia. Aphasic disturbances are frequently absent. The fourth zone includes the anterior part of the inferior-internal surface, and in tumors of this area hallucinations of taste and smell are common.

Arranging the present cases according to Mingazzini's classification, there were two tumors involving zone 1, the first extending beyond the limits of the zone. The case presents so many features of interest both psychiatric and neurologic that it is given in abstract. The patient, a left-handed person, with a left-sided tumor, had also the nearest approach to Witzelsucht of any of the state hospital cases.

Case 1.—*History.*—A woman, aged 35, sent to the Boston State Hospital from a general hospital to which she had been admitted with the diagnosis of hysterical hemichorea, had always been flighty and peculiar. For several years previous to admission she had made no effort to work, but lived on her savings. She complained of numbness in the right hand for two or three years; weakness and tremor of the right arm and leg came on suddenly three months before admission. She had had several slight fainting attacks. On admission she was talkative, hilarious and facetious; her replies were relevant but flippant. She complained of her illness, but was not concerned over it, and showed no insight. She was well oriented for person, place and time; her understanding of surroundings was fair. Remote memory was apparently somewhat impaired; her memory for recent events was good. She would not attempt the educational tests. She had no hallucinations or delusions. She was neat and docile.

7. Knapp, Albert: Die Geschwülste des rechten u. linken Schläfe-lappen, 1905.
8. Aswazoturow: Monatschr. f. Neurol. u. Psychiat. **29**:342, 1911.
9. Mingazzini: Rev. neurol. **28**: No. 13 (July 15) 1914.

Physical Examination.—The face was expressionless. Movements of eyes and tongue were normal. The right pupil was larger than the left; both reacted well. Vision was undisturbed. There was no choked disk. Hearing was normal, and power of speech was intact. The right arm and leg were spastic and atrophic with marked coarse tremor, increaseed on intention. Knee kicks were increased. Sensation to touch and pain was normal.

Course of Disease.—The patient remained at the hospital for two and a half months. She had alternate periods of drowsiness and exhilaration; during the latter she laughed and talked much of her suffering. She had severe occipital headache. The temperature was continuously subnormal; pulse rate, 80-100; respiration, 20-25. Death occurred suddenly in syncope. No definite diagnosis was made, either at the general hospital or at the hospital for the insane.

Necropsy.—Necropsy revealed a very large cholesteatoma, which had destroyed the anterior half of T1 and T2, the transverse temporals, the lower border of Broca's area, the lower part of the insula, the pyriform lobule, the anterior half of the hippocampus and the subthalamic structures on the left.

CASE 2.—*History.*—The second case was an endothelioma involving the anterior part of the right temporal lobe in a woman aged 57. The illness began two years before death with a change of character, the patient becoming moody, suspicious and irritable and showing defective judgment. Weakness of both legs developed into spastic paralysis; she had general convulsions every three or four weeks. In the hospital she had periods of confusion, alternating with comparative clearness, euphoria and facetiousness; also episodes of auditory hallucinosis, to which she responded energetically. Dysarthria, double ptosis and conjugate deviation of the eyes to the side of the tumor were noted. This case was complicated anatomically with cerebral arteriosclerosis.

The tumor involving zone 2 has been reported by Fuller.[10] The growth was on the left, sensory aphasia was prominent, and auditory hallucinosis was mentioned. The neurologic signs were divergent squint, exophthalmos and bilateral choked disk.

The third zone was involved in two instances. The symptoms in the first patient, a man of 57, were nervousness, irritability, insomnia, possibly auditory hallucinosis, right-sided headache, unsteadiness of gait and tremor. The neurologic symptoms were marked exaggeration of all deep reflexes, general increase in muscular tonus, general tremor, right-sided facial spasm and left Babinski reflex. The tumor involved both the third and fourth zones on the right, extending from the tip to the splenium, destroying also the hippocampus, and extending upward, invading the insula and all structures up to the lenticular nucleus.

The second case is taken up in the discussion of tumor in senile patients.

The fourth zone was the site of a tumor in one instance. The patient was an imbecile of 58, who had deteriorated rapidly in the two

10. Fuller: Westboro State Hospital Papers, Series 1, 1912.

years before death. She had olfactory hallucinations, at times calling out continuously, "Oh, that bad smell!" Seven weeks before death she had a convulsion followed by weakness of the right side and involvement of speech. The tumor, a metastasis from a hypernephroma, involved the inferior and mesial surfaces of the left temporal pole.

Each of the cases quoted above presents features of the syndromes of Kennedy, Knapp and Mingazzini, but no one case corresponds closely to any of them.

The only instances of pronounced euphoria in the entire state hospital series are the two temporal tumors mentioned above.

TUMORS OF THE CORPUS CALLOSUM

The two patients with tumors of the corpus callosum, involving the entire length of the structure but not limited to it, showed marked mental changes. In the first patient there was increasing slowness of reaction, with somnolence, but his answers were coherent and relevant, and showed comprehension; recent and remote memory were good and school knowledge was retained. Paralysis of the legs occurred late in this disease. The tumor infiltrated laterally into the right frontal lobe. In the second patent the first and the predominating symptom was loss of memory, which progressed until a few months before death there was absolutely no immediate retention. The patient was confused and completely disoriented. Two months before death optic aphasia was noted. The tumor swept out laterally into both parieto-occipital regions. In neither of these cases was there involvement of the cranial nerves.

TUMOR OF THE VENTRICLES

There were four cases in which the tumor (a glioma in each case) was wholly or almost wholly within the lateral or third ventricles. These cases were characterized by profound mental symptoms, in three cases, prominence of the general symptoms of tumor and abundance of neurologic signs. In two cases there was a gradual failure in all mental functions, without active manifestations, and reaching an extreme degree. The third case was complicated by an independent manic-depressive psychosis. The fourth was characterized by increasing lethargy with transient periods of amnesia and confusion, but without true dementia. There was some similarity in the physical signs, the most prominent being unequal pupils, with sluggish reaction to light, in three cases; exaggerated reflexes in three, spasticity in two, tremor in all, and marked ataxia in three cases. Weisenburg,[11] in his article on tumors of the third ventricle, emphasizes the prom-

11. Weisenburg: Brain **33**:236, 1910.

inence of symptoms of internal hydrocephalus, the marked mental symptoms, the paresis and spasticity, and the ataxia which is present in nearly all cases.

MENTAL SYMPTOMS

It is fair to assume that because they were sent to hospitals for the insane, the patients studied represent a selected group in which mental symptoms were, to the committing physicians, the most prominent feature of the disease.

The predominance of mental symptoms was due, in a part of the group, to a coincident psychosis of one of the common forms. Thirteen of the patients had been recognized as mentally abnormal—either defective or psychotic—before the development of the tumor symptoms. Three were already in hospitals for the insane, and one was committed after operation for brain tumor. In the other instances the primary psychosis caused the patients to be committed. There were, however, well-developed organic signs in all of the latter cases at the time of entrance. The psychoses represented were: manic depressive, dementia praecox, paranoid condition, senile dementia and alcoholic dementia. In three cases, at least, it seemed to be the development of the tumor that precipitated the active symptoms of the psychosis, and thus necessitated the final commitment.

Excluding the cases in which there was an independent psychosis, with its own characteristic symptoms, and those patients admitted with terminal lethargy and somnolence, in a review of the mental symptoms one is impressed by their undetermined character, the symptoms being most frequently a simple deterioration in all mental functions with apathy, varied occasionally by periods of confusion or slight euphoria. These symptoms occurred with tumors in various situations. Hallucinosis was sometimes mentioned, but was not a prominent feature, except in the temporal lobe tumors. Disturbances of memory were emphasized in the majority of cases — most frequently there was a diminution or even total loss of immediate retention; in other cases, transitory periods of amnesia. The memory disturbances were most extreme in a tumor of the corpus callosum and in one filling the ventricles and associated with an extreme increase of intracranial pressure. In the temporal tumors, as mentioned above, emotional changes were prominent. No pronounced depressions, and no neurasthenic, hysterical or developed paranoid states were found.

It appears that this deteriorating tendency which is so prominent in the state hospital group depends not only on the site of the tumor, but is to some extent characteristic of brain tumors in middle life. Of the twenty cases in this group between the ages of 45 and 60, with no independent defect or psychosis, twelve, or 60 per cent., presented

a picture of apathetic deterioration, while of the nine similar cases below 45 years, only three, or 33⅓ per cent., presented a similar picture (two of them frontal tumors). A psychiatric study of a group of young patients with brain tumor in a general hospital would be valuable to contrast with these mature patients. Of the four patients under 30 in the state hospital series, two were imbeciles and the other two were admitted in the terminal stages of the disease. It is precisely these deteriorating, middle-aged patients who would gravitate naturally to hospitals for the insane. This explains why the average age of the state hospital patients is greater than that of brain tumor patients in general.

Schuster goes to considerable lengths in correlating particular mental symptoms with tumors of different regions. We cannot come to any such definite conclusions as he does regarding the association of complex mental reactions with the involvement of certain locations. In fact, the very lack of clear-cut psychiatric pictures is the prominent feature in this series.

BRAIN TUMOR IN THE AGED

There were three tumors in persons 70 years of age or over, the oldest being 86. Only one patient, a man, aged 70, an alcoholic for many years, had symptoms referable to the tumor. On admission he was confused, irritable and suspicious. His answers were incoherent and irrelevant. Recent and remote memory was markedly defective, and school knowledge was entirely lost. There was disorientation for time and place. The physical findings were advanced peripheral arteriosclerosis, emphysema, general hyperesthesia, particularly along nerve trunks, exceedingly active knee jerks and fine tremor of the fingers. The patient had convulsions at intervals of a few weeks during his two years' stay in the hospital. The first of these began in the right arm and leg, but later they became generalized. He complained at first of headache and nausea following the seizures. A year before death aphasia of the motor type appeared with increasing dementia and feebleness. The tumor was a large glioma of the left prefrontal region.

The second case was that of a woman of 72, probably an old dementia praecox, and a hospital inmate for many years. She had had for a long time alternate periods of apathy and extreme excitement, and after one of the latter failed gradually, without special signs or symptoms. The tumor, a glioma, was situated on the under surface of the right temporal lobe, invading also the hippocampus and pyriform lobule. The brain also showed marked arteriosclerosis with small softenings in the thalamus and the lenticular nuclei.

The third case ran its course as an ordinary senile dementia, complicated with chronic nephritis and arteriosclerosis. Mental failure was said to have begun at 75 years. During his nine months' hospital residence, the patient was bedridden, quiet, contented, and completely disoriented for time and place. Recent and remote memory was poor and there was some fabrication. No significant neurologic signs appeared. Failure was gradual. The tumor was a large endothelioma on the orbital surface of the left frontal lobe, protruding into the ventricle. The brain showed the microscopic changes of senile dementia, including plaques.

The reason for the lack of symptoms in some senile brain tumor cases may be that the normal senile brain atrophy lessens the tendency to increased intracranial pressure, and that tumors at this time of life might be expected to grow slowly. In regard to the first point, these senile brains showed flattening of the convolutions only in the vicinity of the tumor and atrophy elsewhere.

It is obvious that brain tumor patients at state hospitals do not in general offer good prospects for operation, on account of the inaccessibility of the majority of the growths, the late stage of the disease, and the frequent complicating factors, especially arteriosclerosis. Nevertheless, decompressive operations would in many cases have added to the patients' comfort. All patients in state hospitals diagnosed as having or suspected to have brain tumor should be examined by a neurologic surgeon, and the possibility of operation considered.

CONCLUSIONS

Brain tumors occur in general hospitals and in hospitals for the insane with about the same frequency.

The group sent to hospitals for the insane is composed partly (30 per cent.) of patients recognized as defective or psychotic before the development of the tumor and partly of those in whom mental symptoms appear with the tumor.

The average age of patients with brain tumor sent to hospitals for the insane—50 years—is greater than the age at which brain tumors usually occur; 68 per cent. of the cases in these hospitals occur in patients between 40 and 60 years.

Frontal tumors predominate, forming 33 per cent. of the cases.

The majority of patients are admitted in the late stages of the disease, and the condition is diagnosed, even tentatively, in only about 25 per cent. of the cases (excluding those admitted to the hospitals with the diagnosis).

The chief reasons for the small proportion of cases diagnosed are that more emphasis is laid on the psychiatric than on the neurologic aspects of the case, that ophthalmoscopic examinations are not made as a routine measure in organic cases, and that, as the majority of the patients are middle-aged or elderly, there are frequently complicating factors, both mental and physical, which would be absent in younger persons.

Cerebral arteriosclerosis is a complication, at least anatomically, in somewhat less than half the cases.

In brain tumor of middle-aged patients committed to hospitals for the insane the usual predominating mental symptoms are simple deterioration and apathy. These were most prominent in the frontal

tumors, but were present also in those of other areas, with the exception of the temporal tumors, in which the symptoms were more active and varied. This tendency to deterioration appears to be especially characteristic of brain tumors in middle age.

The development of a brain tumor may be the factor which determines the onset of an independent psychosis in a predisposed person.

In old age, brain tumors may reach a large size without giving characteristic signs or symptoms. The reasons for the atypical course appear to be the senile brain atrophy counterbalancing the tendency to increased intracranial pressure, and the probable slow growtth of the tumor at this age.

It is earnestly urged that the possibility of brain tumor be more frequently considered in insane patients: that ophthalmoscopic examinations be made in all atypical organic cases, and that when brain tumor is diagnosed, the question of at least a decompressive operation be considered.

POSTBELLUM NEUROSES

A CLINICAL REVIEW AND DISCUSSION OF THEIR MECHANISM

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An experience with the American Expeditionary Forces, which comprised a period of intense study of war neuroses at the special hospitals established for their treatment during and after the war, combined with an opportunity to observe the onset of these disorders while serving with a division of troops that had an exceptionally arduous campaign in the Argonne, has increased interest in such cases now appearing at the War Risk Insurance office and at the office of the Federal Board for Vocational Training. It seems worth while to attempt a brief analysis of some of these patients in order to determine what factors are responsible for the continuance of their invalidism at this late date.

THE RESIDUALS OF HYSTERIA

So far the men with the most pronounced symptoms, such as the residuals of a definite hysteria of long duration, have been almost entirely those who served with the British forces and had been in the trenches for long periods before developing grave symptoms. None of these had received prompt treatment in special hospitals near the front, but had been sent back to the home base before active treatment had been instituted, contrary to the method practiced in the American army during the latter months of the war, when special hospitals with each army corps and specialists with each combat division were functionating. In this connection the writer has noted that the majority of the cases from the American army now being seen are in men who developed symptoms during the early weeks of the American campaign before the facilities referred to were available. This tends to show the value of early diagnosis combined with prompt special treatment of any form of functional nervous disease.

The scarcity of postwar neuroses compared with the frequency of neuroses during the war, and the large number returned to duty either at the front or in the intermediate zone while the war was in progress, is an illustration of the value of accurate diagnosis and treatment in the first stages of the disorder. It may also serve as a commentary on our unhappy methods of handling patients with civil traumatic neuroses, so many of whom drift from one doctor to another before the true nature of the trouble is determined, but not before the neurosis

has become aggravated and firmly fixed by unfortunate suggestions. To be sure, those who develop traumatic hysteria in civil life have not the same incentive to get well that can be given to the patriotic soldier during a critical period of war when his comrades at the front are stemming the onslaught of the enemy. As our compensation laws are at present framed, those with industrial neuroses have a sordid motive for remaining unfit.

Possibly one might think that any case of "shell shock" remaining uncured a year after the armistice is a case of true concussion of the nervous system, a literal shell shock, with permanent organic change in the brain or spinal cord. This is far from the truth. Such cases are very rare. Many cases attributed to concussion have been seen with permanent mental derangement, but their histories show evidence of mental disorder before entering the service, and their symptoms are those of well known psychoses or of psychopathic states inherent in the individual. Those in whom the symptoms can be called the residuals of organic injury are conspicuous by their rarity. Of a hundred odd cases the writer can recall only two of this nature.

FIVE GROUPS OF POSTBELLUM NEUROSES

The postbellum neuroses now being seen can be classified into five groups: (1) primary neuropathic and psychopathic states, including constitutional neurasthenia, psychasthenia, emotional instability and paranoid states; (2) secondary neurasthenic states, that is, neurasthenic syndromes following influenza, pneumonia or other infections, or following prolonged physical exhaustion and complicated by thyrotoxicosis, myocardial degeneration, tuberculosis or amebic dysentery (but of more importance are the neurasthenic syndromes secondary to a definite mental complex, as will be shown); (3) persons simulating illness or exaggerating trivial complaints and attributing them to military service, usually because they wish to take advantage of the provisions of the federal board for vocational training rather than settle down to the old prosaic job held prior to the war. They feel that the country owes them something because their careers have been interrupted. These might be classified as malingerers or as hystericals, according to the charity of the observer; but, in all fairness, it should be stated that many of these men are entirely sincere in their belief that military service and whatever illness they contracted during service has unfitted them for the work they formerly did, and they are also sincere in their claim that the government should help them to a readjustment. This feeling has been largely fostered by the popular press with its articles on the psychology of the returned soldier; (4) uncured hysterical symptoms, and (5) chronic residuals of true cerebral concussion or other forms of brain injury.

The preceding classification has been made in the order of frequency of type seen in the course of examination of several hundred applicants for either compensation or vocational training. All have had a careful physical examination, as well as a neuropsychiatric examination.

Group 1 represents the sort of man who was overlooked by the draft boards or by the examiners at the training camps and who should never have been accepted in the service. Most of these men have failed to make good even at the training camps or in the intermediate zone overseas, and if they have been at the front they have been quickly sent back with an acute neurosis or psychosis. Now that the war is over, they are of course no better than before; they have much difficulty in adjusting themselves to civil life and are inclined to attribute their difficulties to the effects of some trivial illness or to the strain of military life. A few minutes' conversation with them usually suffices to make clear the fact that the trouble is a constitutional one and not acquired.

Group 2 contains two quite distinct types of acquired psychoneurosis: patients who have definite physical disease as the primary cause and those in whom the cause is a mental complex due to individual circumstances and the patient's reaction to them. Both types are found in men who to all appearances have been normal prior to military service and who have done well in the service up to a certain point. To describe in detail the first type is unnecessary, but attention should be called to the fairly large number of postinfectious states following influenza and pneumonia in which the myocardium is inefficient, and to the cases in which disorder of the thyroid is a prominent feature. As to prolonged physical strain being the only factor responsible for a neurasthenic state lasting for a year or more after the strain is removed, the writer is obliged to be skeptical. Even if no mental cause is found it may nevertheless be the main factor and should be persistently sought. The following case illustrates how a mental complex can be the sole cause of a neurasthenic state:

CASE 1.—*History.*—W. C., aged 30, came from intelligent, refined stock and his father had served with credit in the Civil War. The patient had been a successful mining engineer and had never suffered from any nervous symptoms; in fact, he had been particularly apt in mixing with business men and in venturing on new undertakings. He got on well in the training camps and was assigned to a company of engineers sent overseas early in the American campaign. They soon went under fire at Château-Thierry. The patient immediately experienced great fear, and this was intensified when he was thrown to the ground by the bursting of a shell near him. He was not physically injured or rendered unconscious but soon afterward experienced diarrhea and weakness of his legs. He reported to the company surgeon who advised him to go to the hospital. He begged to be allowed to remain in the ranks and as

things quieted down he improved. He continued on duty, although not feeling well, and was given light duties. Then his regiment was sent into the Argonne Forest to prepare for the expected advance. The patient carried on with fear in his heart and apprehension as to how he would endure again being under fire, but he would not admit this to any one nor to himself at the time. Again under artillery fire, he suffered extremely from anxiety whenever he heard the sound of shells, and in the intervals he was so weak from emotional strain that he prayed that the next shell might put an end to his misery. Nevertheless, he refused to ask for relief from duty. Fortunately his officers were lenient and sympathetic and spared him all they could by giving him light duty and allowing him to stay in a dugout much of the time. In this fashion he carried on until the armistice, trying hard to repress the knowledge that he was the victim of miserable fear. Shortly after this he was sent to a hospital because of general fatigue, insomnia and mental depression. Subsequently, while in various hospitals he frequently had crying spells and often dreamed of the war, but was loath to talk about it. However, he could not keep from thinking about it and grieved over its horrors and his comrades who had been killed. He was sent to the United States and was under observation for several weeks. His trouble was diagnosed as psychoneurosis and he was finally discharged from the service with this disability on his record. This was a great disappointment to him, because he had planned to reenlist and try to make up for his failure to carry on well at the front by giving more service to his country. After being discharged he tried to resume his old line of work, but when he approached business men he would become tremulous, his voice would fail and confidence in himself would evaporate. So he decided that the war had done something to him which had left him permanently incapacitated for his former occupations and that it would be best for him to prepare himself by special training for work in which he would be on a salary and not obliged to take much responsibility or initiative. He therefore took up the study of geology in order to prepare himself to be an inspector of mines. But he continued to have headaches and insomnia and found it difficult to concentrate and to get through the day without extreme fatigue. Consequently he failed in some of his examinations and felt that his memory was failing. He had planned to join the American Legion but could not bring himself to mix with former service men, although he was particularly interested in returned soldiers who were not well, especially if they had any nervous troubles. He continued to dream often about the war.

Treatment.—When this patient came for examination, apparently he had no idea of the real cause of his difficulties and gave but a meager history. He did not at this time tell about his reaction when under fire. He spoke of his experiences only in a general way, saying that he had been through a great deal and that the war had caused some permanent change in him both physically and mentally. It was only when his war experiences had been gone over in detail step by step, that the above history was obtained and he admitted that he was unable to get rid of a feeling of shame because of his reaction to shell fire, especially since he was the son of a Civil War veteran. He finally was made to realize that this feeling was the cause of his sense of inadequacy, his preoccupation of mind, his dreams and his aversion to discussing the war with other people. After all his symptoms had been linked up with this complex, it was pointed out to him that only by a different and more reconciled and more impersonal attitude toward his reactions at the front could be bring back his old self-confidence and efficiency, and that to attain

this mental attitude he must see things in truer perspective; that he had really carried on very well, because in spite of great fear with all the physical and mental suffering that such fear entailed, he had had the moral courage to stay in the game and refuse to be sent back to a hospital until the danger was over. He was told that he ought to feel able to look any man in the face with as much equanimity as any returned hero, and that when he really believed this and felt this way about it, he would begin to get well and would recover entirely. At the end of this talk he showed a marked change in demeanor, his face had brightened, his voice was stronger, his gaze steady and he stated that he agreed absolutely with the examiner and expressed great wonderment that the physician had guessed so well his feelings and mental attitude.

Group 4, presenting uncured or relapsed hysterical symptoms such as paralysis, tremors, amblyopia, nocturnal delirium, etc., contains only five cases, and one of these was complicated by residual symptoms of true cerebral concussion. The other four patients revealed either a conscious or unconscious motive for the continuation of their illness, one of them being undoubtedly quite sincere, and the others showing evidence of conscious simulation.

Case 2.—One of these four patients had been entirely cured of hysteria during the period of hostilities and had been returned to duty and carried on well. After his return to the United States and discharge from the service, having found that his sweetheart had married during his absence, he went on a spree and before he was quite sober reenlisted in the army for three years. A few days later all his hysterical symptoms returned, and he was awaiting discharge from the service on a certificate of disability, when the writer saw him. At this time he had improved very much and presented only an emotional state. He was applying for vocational training.

Case 3.—One of the patients in whom malingering was suspected was a man aged 41, who gave a history of having lost consciousness after a nearby shell explosion, which he claimed had caused a fracture of the skull. This incident had been followed by a long period of apparent amnesia, and he declared that he had been unable to move his left arm and hand since he became fully conscious. He was not treated at any of the special hospitals for neuroses but was sent at once to a base hospital, and from there he was passed along through various hospitals unimproved, being frequently examined and hearing his case frequently discussed. When seen by the writer he was found to be very well informed on the effects of brain injuries. He showed a typical functional palsy of the left upper extremity and claimed to have poor vision, spells of brief unconsciousness and what he called "jacksonian attacks" in his left arm, which he illustrated by a jerking movement of the forearm while being examined. But this was not observed at any other time. When asked to show his tongue it deviated far to the right but at another time to the left. He called attention to a supposed depression in his skull, but examination showed only several small sebaceous tumors in the scalp, and the roentgen-ray examination revealed a perfectly normal skull and brain shadow. This man's attitude was persistently surly and uncooperating. He asserted that he had been told that he would get no better and opposed the examiner's views as to the nature of his trouble and the prognosis with arguments based on what he had observed in patients with head injuries in the hospitals he had been in

and on remarks of other physicians. He was opposed to any treatment except an operation on his skull. Finally he was persuaded to enter a hospital and was given daily treatment by physiotherapy and electrotherapy, was handled patiently and tactfully and examined by another neurologist and an ophthalmologist who also assured him of recovery without operation. After a week he had shown no change in his mental attitude, and one day left the hospital without the permission or knowledge of the resident physician, being accompanied by a too sympathetic female relative on whom he relied for financial assistance. In this case we have to consider a true hysteria following a possible slight cerebral concussion, but there are also features in the case that might justify the suspicion of malingering also being present. The idea of being entitled to total and permanent compensation was prominent in this patient's mind, but, on the other hand, he had requested an operation on his skull. Undoubtedly his condition had been aggravated by lack of proper treatment in the early stages of his illness before so many examinations had been made and so many opinions expressed in his hearing.

Group 5.—It is noteworthy that these cases are seldom seen. They present a fairly typical syndrome, consisting of headache, dizziness, especially on change of posture, vasomotor instability and a mental state characterized by complaints of being unable to think quickly or to concentrate, and by excessive and unusual irritability. Furthermore, they give a history of either skull fracture or actual brain lesion from gunshot wounds, followed by immediate unconsciousness, from which they recovered in a few hours, only to relapse again for a brief time. This was followed by a comatose state varied by delirium, which showed a tendency to persist at night for a long time. Many of these patients seemed to recover entirely rather quickly, while others continued to show symptoms even after being returned to the United States. In this connection it should be mentioned that there is such a thing as a "concussion neurosis" superimposed on the syndrome of either a mild or a severe cerebral concussion. Many such cases were seen in France, but it was observed that after a proper explanation of the symptoms to the patient and persistent reassurance as to full recovery, combined with occupational therapy, the disorder cleared up. Regarding the prognosis of more severe concussion cases in which a neurosis is not the main factor, one is obliged to be uncertain until he has followed up the patient for two or more years.

Group 3.—These patients of the third group of the classification require no further comment. Usually they can be persuaded after a careful examination that their claims are unjustified or that their symptoms are not due to military service, and that the best thing for them is to get down to steady work.

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Abstracts from Current Literature

A CONTRIBUTION TO THE PSYCHOPATHOLOGY OF INCENDIARISM. Gustav Bychowski, Schweiz. Arch. Neurol. u. Psychiat. 5:29, 1919.

The bizarre reactions of mentally diseased persons to incompatible situations are well known. Not infrequently there occurs sudden and persistent writing, tearing of clothes, mimicry, etc. The pathologic aspect doubtless lies in the strikingly inadequate means which are adopted by the individual for the attainment of a more or less conscious purpose. Arson can often be interpreted in that sense. The writer reports the case of a 26 year old laborer of bad heredity who, while in the army, developed an extreme dislike toward one of the officers who had reprimanded him. He immediately generalized his hatred and obtained revenge by stealing a surveying instrument from another officer; at trial he remarked that all officers were of the same stripe. He then began stealing other things—such as railroad time-tables—merely to revenge himself on society in general. Doubtless his antisocial conduct depended in a large measure on a marked enuresis, which made him unwelcome wherever he went. In his downward career, he soon found himself working with a large gang of Italian laborers; here he felt compelled to stay. The situation became unbearable. Without apparent reason he set fire to a pile of telephone poles. Investigation showed that he felt that by so doing he would at once be removed from his present locality. His reactions were typically schizophrenic; the nature of his psychic life, influenced by dissatisfaction, led to a transference of his embitterment, in true infantile manner, to his casual surroundings, which he blamed for all of his misfortune. He lacked the courage to leave his position and search for another; while he realized his own weakness, he blamed it on his surroundings. In burning the pile of telephone poles, he attempted to destroy his entire environment and present reality. It seemed as though the posts for a moment appeared to him to be the symbol of the entire situation, which he could thus destroy most thoroughly by fire.

Another case was that of a housewife, aged 39, who, in the past eight or nine years, developed typical neurasthenic symptoms; treatment in a sanatorium resulted in little benefit. She developed an unfriendly attitude toward other persons. She was dissatisfied with her environment and often threatened her husband should he not allow her to leave the place. A neighbor, who was on the lookout for some fruit thieves, on seeing her pass, remarked in a jocular vein, that she probably was not very dangerous. In response, she stated that she might easily become dangerous enough, and that same evening set fire to his barn. On being admonished by her husband, who told her of the serious consequences this act might entail and that she was in danger of being arrested, she declared that she only wished to get away from her surroundings, and broke down in tears when it was decided, on account of her mental condition, that she was not to be arrested. This wish to get away proved, at closer investigation, to be the index of her entire reaction and the nucleus of the psychic constellation which led to the arson. For three weeks prior to this delict, the patient was daily compelled to see these hated buildings in passing along the street; it was also learned that for eight weeks she felt compelled to carry matches, which she had not been in the habit of doing before and for which she herself could see no immediate use.

The third patient, a man, aged 33, showed definite signs of schizophrenia and was, as well, addicted to alcoholism. One night, thoroughly drunk, he returned home where he was denied admittance. After drinking some more he again returned and was again refused admittance. Having tried several times without success, he looked about for sleeping quarters and saw a shed to which he went. This also was locked and, in a rage, he set fire to it. While attempting to set fire to another shed also, he was apprehended. On examination he was unable to state clearly how it all happened, but remembered that he looked into the flames which appeared so beautiful that he sang and danced as though possessed by the devil; he felt that the fire must put an end to everything and while watching the fire felt greatly relieved of an unbearable oppression. In this case we see primarily the motive of revenge which in a true schizophrenic manner was transferred from the brother-in-law who had refused him admission, to other innocent objects.

The fourth case was that of a 40 year old innkeeper, the victim of psychic epilepsy, who repeatedly came in conflict with authorities for adulterating milk. Although twice punished, he developed a feeling of guilt and when again compelled to submit to an examination for this offense, set fire to his house. The insurance was minimal so that he naturally lost a great deal. He had often felt the compunctions of conscience, which he attributed to persecution by the devil himself, and so was often afraid to go to bed at night. The writer does not feel, on account of the lack of complete amnesia as well as the patient's behavior immediately after the fire, that this deed could be attributed to an epileptic psychic equivalent, but that it more nearly resembled the activity of a psychopath. By suffering the loss of personal property, he could more nearly make adequate atonement for his guilt.

The writer discusses the libido doctrine and does not feel that he can agree with this point of view. The relation between onanism and rubbing sticks to start a fire is not convincing, particularly at the present time when matches are in use, and can hardly be related to coitus symbolism. It is true that fire often appears as an illustration in religious doctrines, for example, that of purgatory, and thus serves as a symbol of cleansing. It is possible that this might apply to the last case discussed. The magic power of fire to free the soul from its captivity in the body and therefore to liberate it for a better existence, developed into the sacred ceremony of the funeral pyre. Doubtless vagabondage, suicide and arson are often dependent on the same underlying misadaptation of the patient to his environment.

The author then illustrates two other cases of reaction types which are somewhat different. The first is that of a highly educated accountant. On account of his exceedingly reticent nature, his free time was spent in taking walks and attending lectures. He was, however, unequal to the practical demands of his work and was reduced in his position. He became greatly dissatisfied and abruptly left his work without a word and without drawing a portion of his salary to which he was entitled. He was quite unsuccesful in every attempt he made to secure another position which he felt society owed a man so well trained as he. One afternoon when his funds were exhausted, he selected some stones and attempted to break a large display window across the street. He did this with great deliberation and it required six stones before the mark was reached. During the course of the trial, he said, that in his opinion society owed him a position; he felt that in prison he could get in contact with the best society, without the expenditure of money that would otherwise be necessary.

The last case was that of a 25 year old man with hypospadia. From early youth he was highly sensitive to his deficiency. The resulting self depreciation became so great that he ultimately attempted to escape from his oppressive surroundings, by developing fugues. In the course of these, he stole money, which was spent in his wanderings.

The author concludes by applying these psychologic methods of individuals, as a means of unloading accumulated affect complexes, to nations. The tremendous movements of nations also offer something which appears irrational, unexpected and therefore secret. Revolutions in particular reveal the double character of necessity and premeditation; while always expected, they are always a great surprise, and exceed not only the expectations of the onlookers, but also those of the instigators. The same is true of war. The onus of an unbearable situation accumulates to the point of discharge; wholly unforeseen consequences and excesses result, despite the best wishes and will of the leaders.

WOLTMAN, Rochester, Minn.

TRANSPLANTATION OF PERIPHERAL NERVES. G. CARL HUBER, an abstract presenting the completion of experimental work on peripheral nerve repair reported in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY **2**:466 (Oct.) 1919.

This abstract brings to conclusion the experimental work on peripheral nerve repair reported on in a previous issue. At the time of the former report, in several of the later series, the experiments of long duration had not been brought to conclusion nor had there been opportunity to study microscopically the tissues removed from these and other series. This brief report is thus supplementary to my former report. The series deserving further consideration are especially Series Nos. 11 to 15 of our former report, dealing with stored homo- and hetero-nerve transplants and Series Nos. 16 to 19, dealing with the use of membranous sheaths as wrappings for nerve transplants.

Uniformly favorable results may be reported consequent to use of homo-nerve transplants stored in petrolatum, liquid petrolatum and 50 per cent. alcohol. In each of these series of experiments in animals, kept more than three months after nerve transplantation, functional return was noted in the calf muscles and after four to five months also in the foot interossei muscles. This functional return as evidenced by contraction of the respective muscles on stimulation of the nerve directly, central to the nerve transplant, was checked in sections suitably stained, taken from successive levels of the operated nerves including sections of the regenerated muscle in which new neuraxes within old nerve sheaths were determined. That these new, down growing neuraxes reached the distal nerve segment through the stored homo-nerve transplant was readily ascertained in cross and longitudinal sections of the transplanted nerve segment. The results obtained after the use of stored homo-nerve transplants are quite as uniformly successful as when fresh homo-nerve transplants are used.

The supposition is permissible that in nerves stored in petrolatum and liquid petrolatum at nearly 0 C. temperature, a certain degree of latent viability is retained by the sheath cells and connective tissue cells and the elements of fibrous tissue, though no evidence of the proliferation of the sheath cells could be ascertained, nor of their direct or indirect participation in the down growth of central neuraxes through the transplant. In the case of 50 per cent. alcohol stored nerves, it cannot be supposed that any latent viability is retained by any of the tissue elements of the stored nerve segment. Therefore, there

seemed to be justification for the assumption that hetero-nerve transplants stored in liquid petrolatum and 50 per cent. alcohol would serve the purpose of nerve transplants better than would fresh hetero-nerve transplants. Series Nos. 14 and 15 were instituted to test this assumption, and had not been completed at the time of the former report. The results attained may be summarized by stating that in no instance was successful regeneration through a hetero-nerve transplant stored in liquid petrolatum realized. There was noted a marked retardation in the fragmentation of the neuraxes and the myelin in the transplanted nerves, these possibly offering a mechanical block to the down growing neuraxes. In the series of hetero-nerve transplants stored in 50 per cent. alcohol a limited degree of down growth of central neuraxes through the nerve transplant was attained, though by no means as extensive as when a homo-nerve transplant stored in 50 per cent. alcohol was used.

In Series Nos. 16 to 18 of our former report consideration was given to wrapping an auto-nerve transplant and the central and distal suture lines with a membranous sheath, with a view to preventing the encroachment of the surrounding connective tissue and of retaining down-growing neuraxes within a limited field. Cargile membrane in single layers or several layers was used for this purpose. Untreated Cargile membrane was found to be absorbed too early to be of any value. Alcoholized Cargile membrane was found to remain in the tissues unabsorbed for a period of at least five months. In sections through the field of the auto-nerve transplant wrapped in two layers of alcoholized Cargile, and examined approximately five months after the operation, it may be observed that central neuraxes passing distalward in the connective tissue surrounding the nerve transplant are retained within the limits of the Cargile sheath. They are thus guided toward the distal segment of the resected nerve, while the nutrition of the nerve transplant wrapped in the alcoholized Cargile sheath does not appear to be influenced by the presence of the sheath since numerous down-growing, central neuraxes pass through the nerve transplant to reach the distal segment of the resected nerve. With reference to auto-nerve transplants wrapped in autofascial sheaths, it is of interest to note that even in the longer time experiments the autofascial sheath remained clearly defined and without material absorption for a period of nearly a year after the operation. However, their presence in the tissues appear to incite a proliferation of connective tissue within and without the sheath to such extent as to argue against their use in practical surgery. The nutrition of the nerve transplant within the autofascial sheath does not appear to be influenced materially since regeneration through the transplant was attained in all of the experiments observed for a sufficient length of time to allow it. In the series in which a formalized arterial sheath was wrapped about the auto-nerve transplant and the suture lines, six experiments, it is of interest to note that the formalized arterial sheath remained unabsorbed, embedded in the tissues, without inciting undue connective tissue proliferation, for a period of at least six months. The neuraxes that grow distalward are retained within the sheath and thus guided toward the distal segment of the resected nerve.

As concerns the general question of the value of sheaths wrapped about transplant and suture lines, it may be stated that as a general rule these are not to be regarded as necessary, and while perhaps not harmful they serve no specific purpose. Considered in the light of our experimental work, the use of alcoholized Cargile membrane may be justified in certain cases. There is very little connective tissue reaction consequent to their use; they remain in place unabsorbed for at least five months after being placed in the tissues.

G. Carl Huber, Ann Arbor, Mich.

OBSESSIONS. R. G. Gordon, Seale Hayne Neurological Studies **1**:235 (August) 1919.

Gordon takes his text from Bernard Hart's definition of an obsession: "An obsession is an idea, action, or fear, intruding itself into consciousness in a manner which is felt by the patient to be irresistible. It is an incomplete and imperfect thing recognized by the patient as being in itself inadequate and unsubstantial." In the latter half of the definition is embodied the chief point of difference between obsessions and mere memory preservations, dominating ideas either normal or pathologic and impulsive actions. While one may not be in complete accord with the author's explanation of obsessions, yet his classification of these psychasthenic symptoms is interesting enough to bear repetition. In the first group belong obsessive ideas which may be either systematized or diffuse. The former are represented by the so-called pseudo-hallucinations which the patient himself recognizes as unreal and the latter by paralysis of action resultant on inability to "make up the mind." The second group comprises the obsessional acts which again may be systematized or diffuse. The first may come to the surface as "manias" which consist of endless repetition in a vain effort to secure perfection. Whether the particular act is performed or left undone is dependent on the strength of the propelling and resisting forces of the complexes. "Pacts" belong to the same class as "manias" and consist in the performance or avoidance of some action accompanied by a vague feeling of impending ill if the act is not performed or avoided, as the case may be. They are disguised expressions of repressed conflicts. Diffuse obsessional actions are the emotional crises commonly designated "hysterics" and are the motor expressions of incoordinated mental activity.

In the third group are listed the obsessive fears or more familiarly the phobias. Gordon's idea of the mechanism here at work is best elucidated by citing one of his cases. "A patient had a very painful experience in which he was discovered by his fiancée in a compromising situation, although as a matter of fact he was innocent of any deflection from the path of virtue. In spite of his protestations the engagement was broken off, and as a result he no longer cared for his morals and for a time lived a loose life. A year or two later, however, he formed an attachment for another girl, and coincident with the time of his discovery that he wanted to marry her he developed claustrophobia. This fear of closed places was confined to places where he could be observed by others, such as music halls, restaurants and the like. Inquiry elicited the fact, that when he realized that he wished to marry the second girl, the events of the past few years came up before him with painful intensity and he worried greatly as to how they might affect his future prospects. He shirked facing the problem, as he found these thoughts very painful, and tried to forget; in other words, he repressed the conflict unsolved. It is to be noticed that the most painful memory was that of being found in a situation from which he could not escape, for this had wrecked his former engagement, and in order to escape contact with this specific memory he unconsciously detached the dread which belonged to this specific event and reattached it to a more general situation, in which he felt himself observed in a place from which he could not escape. Directly this was made clear to him the phobia disappeared." In other words, according to the author, a phobia results when the emotional halo which surrounds a painful idea is detached and subsequently reattached to an indifferent experience in an attempt to avoid contact with the painful thought.

Whatever may be the faults of Gordon's reasoning concerning obsessions, it is refreshing to note that he is apparently not dominated by the sex keynote of the freudian school.

STRECKER, Philadelphia.

THE RÔLE OF THE EMOTIONS IN THE GENESIS OF INSANITIES AND INSANITY FROM THE STANDPOINT OF EVOLUTION. I. S. WECHSLER, M.D., J. Abnorm. Psychol. **12**:375, 1920.

The author has performed a distinct service in applying the psychologic principles of William McDougall to the study of the psychoses. He does not reject the abnormal psychology of Freud but properly objects to the attempt made by Freud and his followers to build a system around a powerful instinct, reducing all abnormal mental manifestations to it. The author believes that all the symptoms of "insanity" can be reduced to the simple terms of disturbance in the balance of the primary emotions. He agrees with Morton Prince in that he believes that all sensations and ideas are attached to other ideas and sensations and held in constellations by means of emotional tone which determines the depth and duration of the "clusters." A disturbance of this emotional tone may disrupt the harmony that normally exists between clusters and thus cause conflict which is expressed as psychic disturbance. The author believes that in the normal mind an easy balance is maintained between the various instincts, sentiments and emotions. Every emotion has its opposing emotion, every sentiment its opposing sentiment. If this balance is disturbed the "psychical process" is disturbed. Insanity, therefore, "is a reversal to unbalanced primary instincts and their emotion and sentiments. . . . They seek expression by means of their conative tendency, only there are no opposing emotions to balance them." For instance, "the delusion of persecution may bring out the emotion of fear, without its opposing emotion of anger, and result in cowering, or bring out anger combined with self-assertion, unopposed by fear and subjection and result in positive, active persecutory delusions of the paranoiac." The symptoms of hysteria are produced by an unopposed instinct of imitation, the contrary instinct of self-assertion being absent. These patients have a weak, poorly balanced mechanism for the exercise of their instinctive and emotional reactions allowing some to act unopposed even in response to disproportionately strong stimuli.

The interesting statement is made that the so-called "organic" symptoms of mental disease, such as amnesia, motor or sensory aphasia, are not "insanity" because only symbols are disturbed and not the emotions. No insanity is possible without disturbance of the emotions and the conscious states which accompany them.

The greatest emotional conflict occurs in the evolutionary process that results from the constant striving of the individual against the "species" or "herd." Sympathy is normally a strong innate tendency that ties up the individual to the group. Insane patients have little or no sympathy because only those emotions that strongly satisfy and amplify the ego are found in them. They are concerned only with a struggle against the group and anything opposing this tendency of ego supremacy is destroyed and if the conflict cannot be won, self destruction results as an escape from it. Sex plays a strong part, chiefly in the psychoneuroses, because here occurs the strongest conflict between the individual and the group. The group brooks no trifling with this instinct because it is the means of preservation of the species. As a result the individual loses touch completely with the group to which he belongs and chiefly

in dementia praecox "there is a loss of adaptation to reality . . . the emotions remain purely subjective . . . and the result is either disintegration or the reconstruction of the subjective world without reference to objective reality."

OSNATO, New York.

MOTOR LOCALIZATION IN THE CAPSULA INTERNA. G. BERGMARK. Upsala Läkaref. Förh. **24**:401, 1918.

The classical investigation of Horsley and Beever on localization in the capsula interna of monkeys has also been applied to man and, as we know, their scheme is encountered continually in textbooks and manuals, but no mention is made of the precise information given by these famous investigators as to the different positions of the paths in relation to the knee of the capsule in different horizontal planes. In the case of man there are, as we know, no experimental investigations of this problem. Attempts have therefore been made to prove the applicability to man of the scheme mentioned by means of clinicoanatomic investigations.

Two methods have been used in these attempts. The first consists in the study of degeneration in the capsula interna after limited cortical lesions. In such cases, however, the degeneration in the capsula interna is not confined to certain bundles, but is rather diffuse. This does not militate against the possibility of a motor subdivision in the capsula interna. Mellus found in the monkey, in which we know for certain that there is a motor subdivision of the capsula interna, fairly analogous degenerations in the capsula interna when he had cut out the center either for the thumb or the big toe. He followed the corticofugal paths irrespective of their function. Horsley and Beever, on the other hand, only followed those that could be stimulated electrically. The investigations are thus concerned with two different things. The absence of limited degeneration in the capsula interna in man after small cortical injuries is, therefore, no argument against the possibility of motor subdivision in the capsula interna.

The other method is the study of small lesions in the capsula interna. The occurrence of limited or quite partial monoplegias would be a decided support for a motor subdivision of the capsula interna. The occurrence of capsular monoplegias is, however, a debated question. While, for instance, German clinicians generally recognize this type of paralysis, it is totally denied by Marie and Roussy. Curiously enough, the simple course necessary for the decision of this question, namely, to examine reports of cases of capsular monoplegia, does not seem to have been adopted. The author's examination showed that there was no case of capsular monoplegia to which objections could not be raised. The only case that might possibly be accepted was one given by Dejerine: intense paralysis of the face and, in addition, a slight hemiplegia on account of a small capsular lesion. The practical consequence of this is that brachial or crural monoplegia proves with certainty a supracapsular localization.

This negative result, however, does not definitely disprove a motor subdivision of the capsula interna as one has to distinguish between symptoms of lost function and physiologic localization. We know, for instance, the different cortical centers for the extension and flexion of the fingers, but we never observe cases in which, on account of a cortical injury, the flexion is more injured than the extension. We seem here to have a problem that lies outside the scope of clinico-anatomic investigation.

Author's Abstract.

UN ALTRO CONTRIBUTO ALLA FISIOLOGIA DELL'OCULO MOTORE COMUNE DELL'UOMO. Armando Malagodi, M.D., Riv. di patol. nerv. **24**:99 (June 30) 1919.

The author refers to Luciani's contention and to Bernheimer's experimental work on monkeys as the basis for his belief that the third nerve nucleus has distinct centers for each group of muscles enervated by this nerve. His observation is based entirely on clinical grounds. A third nerve palsy was observed in a soldier who had been injured on the Carso, May 18, 1917, by shrapnel causing a wound 6 cm. long near the lambdoid suture, the bone being exposed. The left cheek and the mouth were lacerated, and there was ptosis with swelling of the lids and some protrusion of the right bulb. There were a divergent squint in the right eye, a left facial paresis and bilateral beginning papilledema. The right pupil was myotic and did not react to light or to painful stimuli; there was no nystagmus. In his discussion, the author makes no anatomic localization of the lesion and does not mention particularly the decreased deep reflexes on the left, nor does he discuss the reason for the left Babinski reflex. There were no sensory disturbances. There was complete paralysis of the right third cranial nerve. This with the left Babinski reflex and the changed left patellar reflex would indicate an anatomic diagnosis placing the lesion at the level of the cerebral peduncles and the exit of the third nerve root fibers, giving a so-called Weber's syndrome. The absence of signs of fillet red nucleus and posterior longitudinal fasciculus injury excludes an injury to the gray matter about the aqueduct or of the central gray matter. The observation, therefore, has only a very doubtful value because the injury was in all probability not to the third nerve nucleus itself. The ptosis had disappeared, August 28, and was the last residual. June 21, the first improvement began in convergence; gradually the pupil began to react to light and accommodation, and finally the ptosis disappeared. From this gradual improvement, the author would draw the following conclusions: First, that there was a hemorrhage in the "central cavity" involving the nucleus of the third nerve; second, that there was no possibility of a root third injury because there was not isolated ptosis; and third, that the lesion must have been a hemorrhage because the gradual absorption explains the regression of symptoms. Why the author leaves out of consideration the undoubted signs of pyramidal tract involvement on the left side and how he explains the exact nature of the lesion or does not explain it rather, is mentioned above. He argues that the respective centers in the third nerve nucleus for each of the eye muscles supplied by it are separated from one another by a considerable distance, the internal recti being closest, the inferior next and the elevator palpebrae last, each of them separate from the other. Despite the fact that the author defends his anatomic findings on purely clinical grounds the futility of such observation must be mentioned.

Osnato, New York.

THE CAUSES, DIAGNOSIS AND TREATMENT OF HYSTERICAL DEAFNESS, WITH NOTES ON THE AUDITORY—MOTOR REFLEX AND THE PSYCHOLOGY OF HEARING. Arthur F. Hurst, Seale Hayne Neurological Studies **1**:279 (August) 1919.

Hurst closely follows Babinski's interpretation of hysteria. Hysterical deafness is, therefore, due to autosuggestion and possibly to heterosuggestion through which agencies the concussion deafness, which often exists at first,

especially in soldiers, is perpetuated as a "functional condition." The mechanism is ingeniously but hypothetically explained on the basis of a failure of cortical attention. In other words, the hysterical individual ceases to listen cortically, so he does not hear sounds which reach his auditory apparatus in the usual manner. "In the act of listening the resistance at various synapses in the auditory path becomes diminished by some such process as a throwing out of dendrons, which brings those of contiguous neurons into more intimate connection. In inattention the synapses are unswitched, the resistance being increased by the reaction of the dendrons."

The author comments on the auditory-motor reflex (jumping, blinking, pupillary dilatation following a sudden noise) and believes he has confirmed clinically the experimental observations of Sherrington and Forbes. This reflex is said to be independent of actual hearing. It is a function of the midbrain, the posterior corpus quadrigeminum and the medial geniculate body being closely concerned in its production, and both its afferent and efferent arcs are subcortical. It is abolished in absolute hysterical deafness.

Hurst is rather too sweeping in his disregard of some of the methods which have been customarily used to distinguish between organic and hysterical deafness. History and associated evidence of hysteria are given very little weight because deafness has "been the only hysterical symptom in the majority of cases" and "occurs most frequently in otherwise normal individuals with no symptoms or history of neurosis." These statements are certainly opposed to the usual experience of neurologists. Hurst further insists that hysterical deafness is the one symptom which persists during sleep and in hypnosis. Some significance is attached to the absence of a change in the timbre and intonation of the voice such as is often witnessed in organic deafness. Bone and air conduction give no information beyond either implicating or eliminating the middle ear. Hurst makes his diagnosis rest almost exclusively on vestibular symptoms and reactions as determined by rotation, heat and caloric tests. These are always normal in functional loss of hearing.

The main therapeutic reliances are explanation, with persuasion and reeducation. An extremely interesting case is cited in which deafness of seven months' duration was instantaneously cured by a "psychic" operation. Air and bone conduction and the auditory-motor reflex which had all been absent appeared within twenty-four hours.

STRECKER, Philadelphia.

LA CHICHA, BEBIDA DE LOS PRIMITIVOS PERUANOS. HERMILIO VALDIZAN, Rev. de Psiquiatria **1**:62 (October) 1918.

The author says that, according to Bishop Lezanaga, the destruction of the Indian element of the population of Peru is due to the nefarious work of the chicha. The chicha is one of the primitive drinks. It is made chiefly from corn, and is very rich in glucose. There are several different methods of manufacturing this beverage. Originally, it had great religious meaning, and was used at some of the festivals when the people would drink a very great amount of it. Many of the tribes still use the early method of preparation, that is, by the human mastication of the corn, which thoroughly mixes the pulp of the corn with saliva. It is then allowed to stand and ferment. When first made, it has small amounts of alcohol, but as often used, it is buried for a number of years, and with the continuation of the fermentation, it becomes strongly alcoholic.

The author of this article has made a study of the relation of the chicha to the alcoholic psychoses. In a review of the patients in the colony at Magdalena, an institution for the insane, he found that there were hardly fourteen or fifteen patients whose ancestors were users of chicha, and he further states that it is not possible to present a single case of "toxiphrenia" due to the drink of the ancient Peruvians. He does, however, present the summaries of five case histories of patients, who were at the institution at the time of the investigation, in whom chicha could be considered as an etiologic factor, although in none of these cases was he able to show that chicha was the only or the chief cause of the psychosis. In conclusion, he says that the rarity of a "toxiphrenic chichica" in a country which is so essentially a consumer of chicha as Peru, and which has no other asylum than that of the Magdalena, is very suggestive. This allows two explanations: either the chicha is perfectly inoffensive, or the chicha, producing effects on nutrition, acts in a different way from the usual agents of alcoholic toxiphrenia.

A side-light on conditions in Peru is obtained in reading the text, as the author states that use of the straight-jacket is one method of controlling excitements in the asylum.

SOLOMON, Boston.

ON THE IRRITABILITY OF THE CEREBRUM IN THE EARLIEST YEARS OF CHILDHOOD. G. BERGMARK, Upsala Läkaref. Förh. **24**: 419, 1918.

In a child, aged 5 weeks, with hernia of the brain, the writer was able to produce, by means of pressure on different parts of the neck of the hernia, twitchings in different parts of the opposite side of the body. Farthest basally was the point of pressure for the face, above it that for the arm, and highest of all the point for the leg, where twitchings could only be produced however, on one occasion. The twitchings of the opposite side of the body were on the whole very similar, whether one pressed on the right or on the left side of the neck of the hernia. By powerful squeezing of the skin above each point of pressure, it became insensitive to the mechanical stimulation. The case was not investigated anatomically, however, and so it is uncertain whether it was the rind or the projection paths that were stimulated by the local pressure. The writer is, however, of the opinion that the case proves with absolute certainty the irritability of the cerebrum at this time, and bearing in mind our deficient knowledge as to the irritability of the cerebrum in the earliest years of childhood, he thought the case worthy of mention.

Author's Abstract.

MICROSPHYGMIA IN IDIOTS. G. LA ROCHE and G. RICHARD, Ann. de méd. **6**:75, 1919.

Microsphygmia is a special and generally permanent condition of the pulse independent of cardiac conditions and characterized by difficulty or inability in feeling the arterial pulsations.

This condition was investigated in a series of seventy-two mental deficients of all types, ranging from 4 to 70 years of age.

The condition is most frequent in idiots (twenty out of thirty-nine). In higher mental types, it was found in but one of thirty-three cases (congenital idiocy, twenty out of twenty-two). These findings coincide with those of Richet and Saint-Girons, who regarded the condition as characteristic of idiocy. A frequent concomitant is ichthyosis (30 per cent.). Acrocyanosis was also frequently found.

The pulsation-amplitude is not the same at all places in the arterial supply of the arm. In some instances the radial pulsation being absent the brachial showed nearly normal amplitude. The difference between the radial and carotid or subclavian was more marked. The heart was normal.

The cases were investigated by means of a Pachon oscillometer.

Experiments with amyl nitrite, the oculocardiac reflex, epinephrin and retropituitrin showed that the condition could be altered by vasodilators and simulated by vasoconstrictors. Richet and Saint-Girons had already proved that the condition was not of local anatomic origin (narrowness of the artery) and had concluded that the trouble was of sympathetic origin. The authors confirm this, and add that it is due to a state of hyperadrenalinemia or more generally speaking, a sympatheticotonia.

KRAUS, New York.

THE BLOOD PRESSURE IN ANXIETY STATES. G. EUZIÈRE and J. MARGAROT, Progrès méd. **34**:477 (Nov. 29) 1919.

The writers claim that in the so-called anxiety states there is a loss of equilibrium between the vagotonic and sympathicotonic nervous system, with the advantage going to the latter. They have chosen to study especially one feature of the sympathicotonic, namely, hypertension, and they give arterial pressure readings in various groups of cases showing anxiety. Their list is large and comprehensive, but as evidence of possible overelaboration of grouping it should be mentioned that it includes simple melancholias, psychoneuroses, true constitutional anxiety, anxiety psychoses, melancholias with anxiety, anxious hallucinatory psychoses of war, hypochondria and neurasthenia. They consider the elevation of blood pressure frequent in all those conditions; that it is in proportion to the degree of anxiety; that it especially attaches to those showing anguish which is well described as the physical element of anxiety. Briefly, their readings range from maximums of from 120 to 180 to minimums of from 80 to 130, and these figures suggest that all observers might not so readily interpret hypertension from them.

They conclude by saying that their findings have more than theoretical interest and suggest as their application the use of endocrine therapy in all anxiety states. They write: "If the anxiety begins, the anguish is one cause of hypertension; (however) the hypertension can in its turn create the anguish and act as the starting point for the anxiety."

DAVIS, New York.

COMPLETE SECTION OF THE DORSAL SPINAL CORD DUE TO CONCUSSION OF THE VERTEBRAL COLUMN: CONCUSSION OF THE VERTEBRAL COLUMN (FRACTURE OF THE TRANSVERSE PROCESSES, D 9 AND D 10) WITH CONSERVATION OF THE LEFT KNEE AND ACHILLES JERKS AND THE PRESENCE OF THE REFLEXES OF MEDULLARY AUTOMATISM EIGHTEEN MONTHS AFTER THE INJURY. G. ROUSSY, M. D'OELSUITZ and L. CORNIL, Ann. de méd. **6**:150, 1919.

These authors quote several articles dealing with exceptions to Bastian's law in complete spinal section.

They cite a case of a bullet wound which caused a fracture of the transverse processes of D 9 and 10, without causing any injury of the bodies of the vertebrae or in any way altering the normal configuration of the spinal canal.

This case report is lengthy but extremely interesting. The death of the patient gave the opportunity for a necropsy, and the lesion of the spinal cord is pictured in the article as are sections of the tissues found in place of the spinal cord (about D 10).

The unusual features were the presence of knee and Achilles jerks, on the left. Severe constipation was present. *Complete* absence of the spinal cord for a distance of 1.5 cm. corresponding to D 10 was found. Below the lesion there was degeneration of the pyramidal tract down to L 2. The anterior horn cells were intact in D 12, L 1, 2 and 3.

The case indicates clearly that Bastian's law has very definite exceptions. It is an interesting example of the focal necrosis resulting from concussion without direct injury of the cord.

KRAUS, New York.

CHEMICAL DIFFERENTIATION IN MACROSCOPIC BRAIN SECTIONS. E. LANDAU, Schweiz. Arch. Neurol. u. Psychiat. **5**:68, 1919.

The efforts of the author were directed to the development of a staining method which will give positive pictures rather than the negative pictures usually employed at the present time. The only known stain which will do this is carmin. As is well known, the gray matter appears rose colored, while the white matter remains relatively unstained. Guizzette made use of the chemical reaction, $2\ Fe2\ Cl6 + 3\ K4\ Fe(C\ N)_6 = Fe7\ (C\ N)\ 18 + 12\ KCl$. Berlin blue results. He places a section into a 2 per cent. solution of potassium ferrocyanid for an hour and later transfers this to a 1 per cent. hydrochloric acid solution. It is seen that within a few minutes the globus pallidus is stained from a sky blue to a deep blue color, while the putamen as well as the entire cortex remains unstained. Guizzette concludes from this, that the globus pallidus, the nucleus ruber, and the substantia nigra contain iron salts.

The author conceived the idea of impregnating the cortex and the component parts of the basal ganglia with iron salts, thus staining these structures blue by means of the ferro salt or red by the action of sulphocyanid, according to the formula, $Fe2\ Cl6 + 6KCNS = Fe2\ (CNS)6 + 6KCl$. This is done by placing sections of the brain into a 2 per cent. solution of Fe2 Cl6 for a few minutes to one hour, washing, and then transferring them to a solution of ammonium sulphocyanid or potassium ferrocyanid. Since the red dye of the former reaction is so easily soluble in water, the Berlin blue reaction is to be preferred. The white matter of the cortex remains almost colorless.

The author states that these sections have proved eminently satisfactory for macroscopic demonstrations. He is attempting to apply the same principle to microscopic preparations.

WOLTMAN, Rochester, Minn.

TWO PSYCHOSES CURED BY INFECTIONS. HENRI DAMAYE, Progrès méd. **34**:501 (Dec. 13) 1919.

The author considers that two recent cases in his experience are examples of a theory first expressed by Regis—namely, the supposedly occasional curative effects on a psychosis of a transient infective disease. His first patient, a soldier of 20, after a psychosis of eighteen months' duration recovered normal mental status coincident with recovery from influenza. His second patient made a similar recovery from a psychosis of seven months' duration contemporaneous with recovery from an anginal infection.

The account of each case is brief and one is not told how they were diagnosed, though it is implied that both were considered cases of dementia praecox. The first case in particular, however, seems properly to belong in the manic depressive group. The author does not emphasize the features of diagnosis, but merely states his belief that in each case the concurrent infection was of actual curative value.

DAVIS, New York.

"EL PSICOANALISIS EN SUS APLICACIONES EXTRAPSIQUIATRICAS." HONORIO F. DELGADO, Rev. de Psiquiatria **1**:78 (October) 1918.

In this article of thirty-three pages, the author reviews and summarizes the theories of psychanalysis, as expounded by Freud. His description of psychanalysis dates to the time in which everything was related to infantile sexual ideas. He gives a clear, concise and simple account of the freudian doctrine of this period. His review considers a large part of Freud's ideas, including his interpretation of dreams, the psychopathology of every-day life, his ideas of the neuroses and psychoses. Then the author of the article goes on to show how psychanalysis has a value in all fields of human interest and endeavor, especially emphasizing its value in the interpretation of legends and traditions, religious phenomena, language, morals, law, art, philosophy, biology and political economy. All these branches, he says, can be illuminated by the psychanalytic method, and show close relation to the psychosexual life. He concludes by saying: "The things which we have just contemplated bring to the spirit a conviction that we are in the midst of a great revelation. Freud is the explorer of the world of the mysteries of the soul." This article is no new contribution. It is merely the author's presentation of his ideas concerning the freudian psychology. As is quite evident, he is a very enthusiastic follower of Freud.

SOLOMON, Boston.

LEYENDA DE LA GENESIS DE LOS AMUESHAS (FOLK-LORE INDIANO). DR. JULIO C. TELLO, Rev. de Psiquiatria **1**:51 (October) 1918.

"This tradition," according to the contributor, "is of great psychological interest, not only from the general point of view of folk-lore, but from the particular point of view of aboriginal mythology." This myth deals with the development of the worship of the sun and moon among the tribe of Amueshas. It is a very pretty bit of folk-lore, written with a distinctly literary flavor. However, it does not seem to have any especial relation to modern beliefs, nor does the contributor attempt to link it up in any way with psychiatric, neurologic or any broad medical interest.

SIMILARITY IN THE STRUCTURE OF RELATED HEMISPHERES. ZDRAWA JATSCHEWA, Schweiz. Arch. f. Neurol. u. Psychiat. **5**:56, 1919.

The writer attempts to solve the question as to whether the principle of bilateral symmetry of the body can be applied to that of the convolutions of the brain, which, as is well known, show some variations. Occasionally there is almost exact symmetry; in the majority of instances, however, this is not true and it may be hard to discover even a remote similarity in the related hemispheres. On the basis of an investigation of the brains of twenty human beings, eight chimpanzees, two elks, one lion, and four ferrets, he concludes that the principle of bilateral symmetry in the anlage of the convolutions can be demonstrated.

His investigations showed: 1. In some brains the sulci and gyri of both hemispheres are symmetrically developed in one part or another. 2. In that hemisphere where no corresponding superficial gyrus is found, one can demonstrate a more deeply lying gyrus. 3. One may find an excessive growth of a corresponding gyrus. 4. Sometimes opposite convolutions are subject to angulations at a corresponding point; however, this occurs in such a manner that on the one side the direction may be forward, while on the other it is backward.

WOLTMAN, Rochester, Minn.

CONCERNING THE TIME CONCEPT AND A PECULIAR DELUSIONAL CONCEPTION OF TIME IN SEVERE CASES OF TYPHOID.

Professor ADOLPH STRÜMPELL, Neurol. Centralbl. **38**:642 (Oct. 16) 1919.

Our concept of time depends on a fusion of present conceptions with the memories of past events, and it follows that our judgment of time is most accurate when the preceding intervals are short and form an uninterrupted association with the present event. All previous thoughts and experiences have time relations which are dependent on a logical estimate of many differently related circumstances. Of the many factors which may disturb the conception of time, the author cites the influence of the typhoid toxin on four patients, producing a peculiar fixed delusional judgment of time. A girl aged 26 had a high fever and delirium, and after the third week became feverless and rational, other than to insist that she had been in the hospital for seventeen years, that her age was 43, that the last temperature was taken a week before, and other over-estimates of time which persisted for about three weeks, when she suddenly perceived her error.

A woman, aged 40, had a severe case of typhoid and in the ninth week, when otherwise mentally clear, suddenly asserted that she had been sick for two years, considered her age to be 42, was confused about the year, and otherwise magnified the time intervals for eighteen days.

Two other patients showed like disturbances. The author finds it difficult to explain the development and persistence of this delusion, but suggests that the unconscious lapse of time during the delirium, the toxemia, and the protracted stay in bed produced excessive and delusional estimates of time.

SHELDEN, Rochester, Minn.

ON THE CLASSIFICATION OF NERVOUS AND MENTAL DISEASES.

SAMUEL T. ORTON, Am. J. Insan. **76**:131 (Oct.) 1919.

And now comes another classification. Orton appeals to logic, and is not insistent on pigeonholing all cases but on putting a minority in unassailable positions.

Etiology is given first rank as a classifying factor, with groups: (1) infective, (3) toxic, (4) defective and (6) environmental. Group 2, destructive, needs the explanations which are furnished by its subheadings: traumatic, hemorrhagic, anemic, neoplastic. Group 5, metabolic, is complicated and includes errors of food intake and disturbances of endocrine glands not derived from the alimentary tract. The anatomic or physiologic localization is given second place as a classifier, the terms being written against the etiologic subgroups. Clinical entity comes last, instead of first as usual.

So a case is first classifiable as destructive (hemorrhagic), then as encephalorrhagia, and lastly as motor aphasia; or it is first classed as metabolic (dietetic), then as neuritis and finally as beriberi. Manic depressive psychoses and dementia praecox are in the overflow group because the two important classifiers are missing.

This classification, while a valid attack on the standard classification, is not meant by its author to delay the adoption of that scheme by physicians. The very adoption of a first standard makes more easy its replacement by a better second classification, to which Dr. Orton and others are looking ahead.

BOND, Philadelphia.

THE INFECTIVE FACTORS IN SOME TYPES OF NEURASTHENIA. W. FORD ROBERTSON, J. Ment. Sc. **75**:16 (Jan.) 1919.

Robertson is convinced that chronic bacterial infections are an important element in the etiology of neurasthenia. The nasal passages, the lower respiratory tract, the nasopharynx, the mouth, fauces, the intestinal and genitourinary systems were investigated in sixty-six cases. The *B. influenzae*, the pneumococcus, several strains of streptococci and diphtheria bacilli were isolated and cultured. The logical path of such investigation leads to therapeutic immunization, of which the author writes in glowing terms. For instance, six of the group of seven patients, in whom the *B. influenzae* was discovered, made complete recovery under this form of treatment.

At the present time the question of chronic bacterial infections in the psychoses and neuroses is occupying much attention in this country. There can be no valid objection to what may be termed the bacteriologic method of approach, providing that each study is rigorously controlled and that the conclusions do not exceed the premises. With increasing perfection of technic and conservative, unbiased analyses we may reasonably look for much valuable information.

STRECKER, Philadelphia.

DE L'EPILEPSIE LARVEE. R. BENON, Progrès méd. **34**:435, No. 44 (Nov. 1) 1919.

The writer discusses the question of epileptic equivalents and takes the attitude that, while they occur, they are extremely rare. He believes that the symptom which is fundamental for diagnosis is a lacunar amnesia, which is anterograde, though sometimes slightly retrograde. The writer then emphasizes that such an amnesia is readily simulated, and cites at length a case in which the motive for simulation was to escape punishment for theft.

DAVIS, New York.

CHEMICAL ANALYSES OF TWO PATHOLOGICAL HUMAN BRAINS. C. G. MACARTHUR and E. A. DOISY, Am. J. Insan. **76**:159 (October) 1919.

MacArthur and Doisy report a comparison chemical analysis between two pathologic and three normal human brains. The first specimen was from a paretic; the second from a case of bulbar palsy (?). The cerebellum, the brain stem including medulla, pons, midbrain and thalamus, but more particularly the cerebrum, were studied. The pathologic brains, especially the paretic, one showed a marked loss in lipins (14 per cent.) and extractives. The

greatest decrease occurred in the cerebrosids which are closely associated with sheath development. The phosphatids and sulphatids were both lessened. The changes were prominent in the cerebrum, midbrain, medulla and pons, but insignificant in the cerebellum. The clinical diagnosis of "probably bulbar paralysis" in one of the cases must be questioned in view of syphilitic history, a paralytic attack, marked speech defect, assymetric pupils, hallucinations and defective memory. These symptoms seem to be stronger evidence of paresis or at least of cerebral syphilis than of bulbar palsy, particularly when "paralysis of the larynx and laryngeal disturbance" is the only clinical evidence cited in favor of the latter.

STRECKER, Philadelphia.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

J. Hendrie Lloyd, M.D., *President*

Regular Meeting, Dec. 19, 1919

A CASE OF ASTASIA-ABASIA. Presented by Dr. C. W. Burr.

Dr. Burr presented a man, 52 years old, suffering from hysterical astasia-abasia. The patient's early history showed nothing of importance. He had never been a heavy drinker, but had taken some whisky or beer daily for years; he denied venereal infection and his blood Wassermann test was negative. The only nervous shock that he had ever suffered occurred just before his present trouble. He lost $300, all the money he had saved up, by investing it in an unsuccessful junk shop. Immediately after this loss he began to complain of difficulty in walking and in a few days went to bed. On admission to the hospital, Dec. 5, 1919, he was bedridden, not because of a paraplegia but because ataxia prevented standing or walking. On voluntarily lifting his legs from the bed violent ataxic movements started and his malleoli struck together with such force as would cause, in a healthy man, unbearable pain. On the other hand, he had no objective disturbance of sensibility anywhere on the body. On the legs, as everywhere else, he responded normally to touch, pain and temperature stimuli. He localized touch well. There were no motor disturbances in the arms. He had good control of bladder and rectum. The knee jerks were large and quick but not spastic. All other reflexes were normal.

In the left eye there was slight contraction of the field for white and marked contraction for red, blue and green but no reversal. In the right eye there was no contraction for white. For other colors the contraction was the same as in the left eye. The pupillary reflexes and the eye grounds were normal in both eyes. In a few weeks he recovered. The only treatment given was encouragement, with reeducation by making him walk, first with crutches, then with two canes, then one cane and finally without aid.

The case is interesting first, because hysteria rarely appears for the first time so late in life; hysteria is essentially a disease of adolescence and early maturity. Second, when hysteria does begin late in life, ataxia is much more common than hysterical palsies, convulsions and anesthesia.

DISCUSSION

Dr. Francis X. Dercum said that Dr. Burr's patient reminded him of the case of a man whom he had shown at the Neurological Society a good many years ago and in which the etiology was similar. The man was a waiter at a hotel; a fellow waiter robbed him of a considerable sum of money and subsequently he developed astasia-abasia. He was afterward at Blockley where he remained the greater part of a year. Dr. Burr will probably recall a case that Dr. Gilpin showed before the Neurological Society a few months ago; a man who was beyond middle life, developed astasia-abasia after a fall. The symptoms persisted, it would appear, because of the compensation element present.

CASE OF DYSPITUITARISM. Presented by Dr. Frederick H. Leavitt.

A girl, 15 years of age, from the service of Dr. C. W. Burr at the Orthopedic Hospital, at the age of eight months, according to the mother's statement, had had meningo-encephalitis. Since then she had shown evidences of disordered metabolism and physical signs suggestive of a pituitary disorder, as well as palsies and other sequelae of the acute encephalitis. The problem was to ascertain which of her symptoms were due to the endocrine disturbance, and whether the acute infection was responsible for this dysfunction of the pituitary or whether it was a congenital condition.

History.—The history of the case, as well as could be derived from the mother's statement, was: The patient was the youngest of three children. The first was well and married. The second child died at 15 years of age of endocarditis following acute articular rheumatism. The third was born at term by an instrumental and very difficult delivery. She was breast fed and apparently quite well until 8 months old. (At that time the baby was able to stand alone and to take an interest in her surroundings.) She then developed high fever, progressive emaciation and generalized convulsions continuing over a period of three months. When the convulsions ceased it was observed that she was completely paralyzed in both legs and arms. This condition persisted for some months and then power began to return gradually, first in the arms and later in the legs, but she has never been able to walk or to stand since this illness. As the patient recovered the mother noticed that she began to grow fat and that her head seemed to enlarge out of proportion to the rest of her body. At 5 years of age she was very fat and her breasts were very large, almost equaling their present size. The menses started at 12 years of age; they have always been regular, twenty-eight day intervals, of four days' duration and good flow. Pubic and axillary hair started to grow profusely at 14 years of age.

The patient had always been retarded mentally. She had had no teaching either private or public because the mother was told the child never could be taught. She had had no convulsions since her illness. In her diet she preferred red meat, and cared very little for sugar. She always took her tea and coffee without sugar, and she did not care for cake, pie or candy and very little for ice-cream. Pickles and sour things were her preference.

The family history, so far as known, revealed no hereditary taint of mental or nervous disorder. She had had measles at 3 years of age, but no other disease since the convulsive fever when 8 months old.

Examination.—The patient was in bed. She was unable to get out of bed, to walk or to stand, even when her body was supported. Voluntary movements of the hips, knees, ankles and toes could only be weakly made. There was marked flat-foot on both sides. All long bones of both arms and legs were disproportionately short as compared to the trunk. The patient was very fat and of an adiposo-genitalis type. Her head was large and round (circumference 24½ inches), and covered with an abundant growth of well nourished, coarse, dark brown hair. The teeth were very poor in calcium salts. There was considerable fine tremor in both hands, and their coordinated movements were awkwardly performed, probably to some extent the result of the almost complete lack of any training in using her hands. The fingers were short and stubby and there was hyperextension at the interphalangeal joints. At the level of the seventh cervical vertebra there was a false kyphosis. There were no sensory disturbances. The right knee-jerk was smaller than the left but both

were much reduced. Stroking the sole of either foot caused at times a fanning of the smaller toes and dorsal extension of the great toe, at other times a plantar flexion of all the toes. Heart action was rapid (112) and regular, the sounds were very much muffled but no murmurs were audible. The blood pressure was: systolic, 98; and diastolic, 60.

Mentally the patient was very deficient. She could neither read nor write, nor even hold a pencil correctly in her hand, and her attempts at copying plain figures were complete failures. She was overly affectionate and amiable and her true mental condition was partly veiled by a silly pertness.

The body measurements were: weight on admission, 138¾ pounds; height, 53 inches; reach of arms, 58 inches. The eye examination was made by Dr. H. M. Langdon, who reported that the visual axes were diverged but could be brought to parallelation on effort. The motions were full and equal, with a tire nystagmus at the limits of lateral excursion. The pupils were 3½ mm. in diameter. There was fair but slow reaction to light, better to accommodation. The media were clear, the disks were oval and quite pale, with distinct loss of capillarity. The margins were well defined. No other fundus changes were found. Diagnosis: suspected primary optic atrophy.

Roentgen-Ray Report by Dr. Ralph Bromer: Examination showed a sella turcica of rather smaller area than normal. Anterior and posterior clinoid processes were somewhat more closely approximated than usual. The tables of the skull were thin. The bones of the hands showed a fusion of the epiphyses with the diaphyses, which usually occurs about the seventh to the eighteenth year. As the patient was 15 years old this was a rather precocious condition. Examination of the teeth showed an unerupted left upper incisor. Deciduous teeth were also present.

Blood Examination: Hemoglobin, 95 per cent.; white blood cells, 8,000; red blood cells, 4,800,000. The blood Wassermann test was negative. The blood sugar test: fasting, level, 0.076 per cent.; after ingestion, level, 0.085 per cent. (sugar tolerance much increased). Carbon dioxid content of the blood: alkalinity was slightly decreased; the alkaline reserve was practically normal—8.4. The coagulation time of the blood was 4 minutes and 58 seconds. Epinephrin test (Goetsch's): Temperature before injection of epinephrin, 98; pulse, 108; respiration, 22; half an hour after injection, temperature, 99; pulse, 116; respiration, 24. The urine after injection showed no glycosuria. Sugar Tolerance: 200 gm. of sugar, ten specimens taken at hourly intervals—a slight trace of sugar was found in the last specimen; 225 gm. of sugar, ten specimens taken at hourly intervals—a slight trace of sugar was found in the last specimen. The urinalysis was negative.

Summary.—From the history, the child seemed normal prior to the onset of the meningo-encephalitis. The weakness of the arms, legs and eye muscles, the tremors and incoordination of the hand movements, the size and globular shape of the head and the retarded mental development were undoubtedly the result of this infection. The symptoms generally recognized as those of a dyspituitarism were the noticeable features of the case; namely, the disposition of fat of an adiposo-genitalis type, the primary sexual precocity and later suppression, her overly affectionate and amiable disposition, the poor calcium metabolism, abundance of well-nourished hair, tachycardia and low blood pressure and the size of the sella turcica, as shown by the roentgen ray. The laboratory findings, especially the increased sugar tolerance, the decreased akalinity of the blood and the slight lymphocytosis, were also corroborative of a pituitary disorder.

Dr. Leavitt said it was impossible to say whether the moderate internal hydrocephalus resulting from the attack of meningitis caused disease of the pituitary, or whether the disorder of that gland was congenital and developmental. The explanation might be that an inflammatory exudate around the pituitary had caused disturbance of its function.

Dr. Leavitt was unwilling in the present fragmentary state of his knowledge to venture an opinion as to whether the anterior or posterior part of the pituitary was most affected, but the clinical picture was that of an hypopituitarism.

A CASE OF CHARCOT-MARIE MUSCULAR ATROPHY. Presented by Dr. George Wilson.

M. R., a woman, aged 56, single, was admitted to the Philadelphia General Hospital in 1914, and is at present on the service of Dr. William G. Spiller. The woman's condition had been present for a great number of years. Her brother said that it began at the age of six and that it had slowly progressed until 1914 when the patient became bedfast and developed incontinence of urine and feces; one month after these symptoms appeared the Philadelphia Hospital was sought as a haven. As far as the brother knew, his sister had had no pain.

The family history was negative; three brothers and one sister and all their progeny were well.

Examination.—The woman was bedfast. Mentally she showed a mild grade dementia. The pupils were contracted, irregular and did not react to light but came down well in accommodation. The optic nerves were normal. The ocular and other cranial nerves were normal with the exception of the auditory nerves, there being a moderate degree of deafness. No speech disturbance was noted.

The hands, forearms, feet and legs were markedly wasted. The hands were in the claw position and the feet were contracted into an equinovarus attitude. The great toes were similar to those seen occasionally in Friedreich's ataxia. The arms, shoulder and pelvic girdles and the thighs were well preserved. The degree of motor power present was in direct proportion to the amount of muscular tissue left. Fibrillary tremors were not observed. The deep reflexes were absent; plantar stimulation produced no response on either side. Sensation was apparently intact in all its forms. There was a considerable kyphotic curve to the spine. The median nerves appeared to be enlarged to palpation. None of the nerves were tender to pressure. The electrical reactions showed loss of reaction to faradism in many of the atrophied muscles.

Dr. Wilson said that in view of the rarity of Charcot-Marie atrophy he thought it well worth while to present the case to the society. Furthermore, the woman had some unusual manifestations. The Argyll Robertson pupil is occasionally seen in this type of disease. Incontinence of urine and feces and dementia are very rare. If the nerves were really enlarged it would make one think of the chronic hypertrophic interstitial neuritis of Dejerine and Sottas; that disease is supposed by some to be a special type of Charcot-Marie atrophy.

DISCUSSION

Dr. John H. W. Rhein said that he was struck with the resemblance that this case showed to the appearance presented by the rheumatoid arthritis. The deformities in the knees, ankylosis of joints, the appearance of the skin, which he had seen very often in rheumatoid arthritis, were very suggestive. There were the curious choreiform tremors of the arm which he had not seen in cases

of the Charcot-Marie type of atrophy. It would seem to him that the case was one in which the atrophy was perhaps complicated, it might be with rheumatoid arthritis.

Dr. C. S. Potts said that he had found this woman in the ward several years ago and had examined her carefully. At that time he stated that clinically she appeared to be a case of progressive neuritic atrophy or the Charcot-Marie Tooth type. A history of the time and manner of onset was lacking and not obtainable from the patient, owing to her mental condition. He did not think that Dr. Rhein's idea that the patient had arthritis deformans was tenable. The patient, so far as Dr. Potts knew, had never had pain or tenderness of the joints. There was some ankylosis, but this often occurs when the limbs are maintained in one position for a long time, owing to paralysis or the unopposed action of normal antagonists. It should also be borne in mind that there are changes in the electrical reactions, the atrophied muscles not responding to the faradic current.

A CASE OF JUVENILE TABES WITH AN ARTHROPATHY OF THE RIGHT HIP JOINT. Presented by Dr. Francis X. Dercum.

G. B., a girl, aged 14, a native of Philadelphia, attending school, was admitted to the Jefferson Hospital Nov. 2, 1919, with the statement that she had suffered from an injury to the right hip.

History.—The mother died of tuberculosis; the father was said to be well but an opportunity of examining him was not afforded. The patient did not recall having had any of the diseases of childhood except whooping cough about three years before; in 1916 she had a tonsillectomy. She suffered from influenza in 1918, but apparently had not been very ill. Menstruation occurred February, 1918, but was not established until April, 1919, and had been regular since. She also gave a rather unsatisfactory account of having had "stomach trouble" in May, 1919, for which she was treated at another hospital. Later she said something about having received injections by the veins.

Present Illness: About seventeen days before admission, while taking the class exercise in school and while flexing the trunk to the left, she heard a crack in the hip but felt no pain. She first came under the care of Dr. Rugh in the orthopedic service of the hospital, who made the diagnosis of an arthropathy and transferred her to the ward for nervous diseases. Her condition is at present about the same as on admission. The child limped on the right leg, presented an undoubted ataxia in her gait and also a plus sway with the Romberg test. The knee jerks were absent, the pupils were irregular and fixed to light, the left being much larger than the right.

Examination.—The general visceral examination revealed nothing of significance. A roentgen-ray examination showed a marked distortion of the acetabulum on the right side and irregular deposits of bone salts in the soft parts well below the acetabulum. There was also a fracture through the acetabulum. The head of the femur itself was not involved. The appearance was that of a Charcot joint in which there had been a fracture. The serologic examination of both the blood and spinal fluid yielded a positive result.

Juvenile tabes on the whole is quite rare as are also Charcot joints in patients so young as the one presented. For these reasons Dr. Dercum regarded the case as unusually interesting. The patient is being treated at present by mercurial inunctions and by spinal drainage.

DISCUSSION

DR. J. HENDRIE LLOYD said that he recalled that in the early days of the Neurological Society he brought before it a young girl who was under his care in the Home for Crippled Children. She was afflicted apparently with the form of muscular dystrophy known as the pseudo-hypertrophic type. She had marked atrophic arthropathies of the elbows. They were almost like those seen sometimes in locomotor ataxia. It was before the days of the roentgen ray and laboratory tests. Dr. Lloyd thought it was a novel case because in his observation arthropathies in muscular dystrophies must be rare. The case, as he recalled it, had little about it to suggest tabes, but if such a case were to recur now he would, of course, submit it to the laboratory tests for hereditary syphilis.

A CASE OF HEMIPARESIS WITH CHOREIFORM MOVEMENTS.

Presented by DR. ANDREW H. WOODS.

The patient was presented because the involuntary movements of the paralyzed limbs conformed with unusual detail to the type of choreiform movements.

History.—H. B., a man, aged 51, was from Dr. Spiller's wards in the University of Pennsylvania Hospital. Four years before he suffered what was probably a thrombotic affection in some part of the brain, several weeks after which he noticed slight weakness in the right limbs. His eye movements and visual fields were normal. The facial muscles showed no weakness. The tendon reflexes were over-prompt, those of the right limbs being exaggerated. Muscle-tone was increased in the quadriceps extensor, hamstring and calf muscles of the right lower limb. There was a variable patellar clonus on the right; and the right plantar reflex was extensor in type. Power was only slightly reduced in the affected limbs. There was no ataxia. He could thread a needle deftly with his right hand. Light touch and pinprick were perceived promptly in all parts, and there was no spontaneous pain.

There were involuntary movements affecting all parts of the patient's right upper limb, and affecting only the toes and ankle of the lower. These movements ceased when the limbs lay relaxed on the bed; the movements were less marked when his attention was drawn to them, and stopped altogether when he put the parts to voluntary use. After a period of such inhibition, they could be brought out in exaggerated form by causing the patient to fix his attention on the performance of some other act, such as standing on one foot.

Cause of Choreiform Movements.—It would add to the clearness of case reports if the words tremor, choreiform movements, and athetoid movement had standard definitions. The essence of a tremor, as pointed out by Gordon Holmes, is that the affected part oscillated rhythmically, moved by alternate contractions of groups of muscles and their antagonists. Choreiform movements are irregular as to interval, and so have no rhythm; each appears suddenly and passes quickly. Repose of body and mind as a rule quiets them, and they increase with excitement or voluntary effort. But, more rarely, voluntary use of the affected limb will steady it and for a time reduce the muscular contractions. In type they resemble the movements of gesticulation, grimacing and attitudinizing. Athetosis differs from choreic movements in the gradual onset of each individual movement and its slower evolution. A slow tide of tone appears in a group of muscles, rises, then disappears. It may not even produce an overt movement of the part into which the muscles are inserted—the "spasmus mobilis" often described. In type, athetoid movements remind one of the contortions of a person in agony.

The seat of the lesion responsible for the movements in Sydenham's chorea in the large literature on the subject remains a matter of speculation. The optic thalamus is now generally credited with playing an important part on the afferent side in determining the affectual element in sensation; while on the efferent side it possesses centers for the automatic expression of affectual states. The present trend of theory, therefore, prepares us to expect that involuntary movements of the kind now being considered might be due to derangement of this organ. It is unlikely that the causative lesions are irritative, since the resulting movements regularly appear as relatively late symptoms; that is, after the irritative period has passed; and continue indefinitely thereafter. Walshe's contention based on his study of the work of Sherrington and others, seems valid, that the basal ganglions being phylogenetically older than the cortex are probably subject to inhibition from it, but have not control over it. It accordingly seems safer to suppose the lesion is a negative one, that is, a lesion which subtracts the action of some mechanism, and as a result allows some lower mechanism to function without normal control. Holmes' own cases and the review made by him of sixty cases published by others, the experimental work of Sherrington and his collaborators, the recent reports by Wilson and others on lenticular disease, and many cases showing the association of optic thalamus lesions with these involuntary movements, the very apposite study of Rhein of a patient with lenticulo-rubro-cerebello-olivary degeneration, and the findings of many others, all point to the basal ganglions as responsible for athetoid movements, and to lesions in or near these ganglions or their congener, the red nucleus, as responsible for choreiform movements. Tremors have been found associated with lesions in any part between the internal capsule and the medulla oblongata.

As to the exact mechanism, we are left to choose between two general classes of theories: In one class a negative lesion in the tracts connecting the basal ganglions, red nucleus, cerebellum and spinal motor centers disturb a normal balance between the functions of those several parts and that of the corticospinal system. As a result, these complex movements result. In the other class the basal ganglions, particularly the optic thalamus, are regarded as possessing centers whose positive action produced movements fitted to express emotion and which are controlled by the cerebral cortex. In these patients, lesions near the basal centers cut tracts by which the cortical control is normally effected, and thus allow the automatic centers unregulated sway over the muscles involved.

DISCUSSION

Dr. John H. W. Rhein said that he had seen the patient presented by Dr. Woods at the Polyclinic Hospital on a previous occasion. The movements that this patient presented were similar to those in a case reported by Dr. Potts and himself some years ago. Dr. Rhein said that he had not seen the patient but had studied the brain and spinal cord.

This man's symptoms began with weakness and numbness in the legs which never progressed to a great extent. Later there was difficulty in writing, some incoordination of the upper limbs and a tremor, which was to and fro and constant, in the right arm. The knee jerk on the right side was increased. Otherwise, the reflexes were normal, the Babinski phenomenon being absent. The pupils responded sluggishly to light.

At the necropsy, a bilateral lesion of the lenticular nucleus in the putamen was found. In the left putamen, the lesion was in the posterior portion; in the right putamen, it was in the middle portion.

Dr. Rhein stated that he reported a second case of posthemiplegic tremor in a woman of 43 at the Home for Incurables. At the age of 9, following a convulsion, there was a loss of power in the left arm and leg. A clonic contraction of the muscles of the paralyzed members developed. In the hands it resembled pill-rolling movements seen in paralysis agitans. In the legs the movements were to and fro. The reflexes were disturbed very little, the Babinski phenomenon being present.

At necropsy there was found an intact pyramidal tract on each side and a very small lesion in the lenticular nucleus on the left side. Microscopic study showed degeneration of the right ansa lenticularis, the right red nucleus, the left superior cerebellar peduncle, the left dentate nucleus, both inferior olives, the left being totally degenerated and the right to a slight degree, and finally the right restiformis was smaller than the left.

The cases showed what has already been described but not histologically proved, namely, the anatomic connection between the dentate nucleus through the superior cerebellar peduncle with the contralateral red nucleus and the lenticular by way of the ansa lenticularis.

Dr. Rhein believed that this connection, which he termed the lenticulo-rubro-cerebello-olivary tract, constituted the underlying pathologic basis for extrapyramidal motor disturbances. A lesion in any part of this tract, in his opinion, might give rise to a disturbance of motion of the extrapyramidal type. The case was somewhat confirmatory of the position taken by Dr. C. K. Mills, who explains motor disturbances through the intermediation of the cerebello-rubro-thalamo-cortical apparatus and the cerebro-rubro-spinal apparatus, asynergic phenomena resulting if the cerebellar influence is withdrawn, hypertonicity and involuntary movements if the tonectic excitation from the striatum is withheld.

Most hemiplegic movements such as tremors, choreiform movements and the like have been described in cases in which lesions have been found in the thalamus with or without involvement of the caudate nucleus.

In some cases, the lesion is in the crus-cerebri; in others, in the cerebellum and in still others in the superior cerebellar peduncle, red nucleus and tegmentum; in others the cortex has been implicated, and finally in some cases the cord is the seat of the lesion.

Various theories have been advanced to explain the origin of the movements. Some advance the theory that the optic thalamus is the coordination center. Another theory is that the corpus striatum inhibits movements and that the thalamus organizes movements, and that a lesion of the corpus striatum produces lowered inhibition. The theory that Charcot advanced that there was a chorea bundle has long since been abandoned. The theory that it is due to an irritation of the pyramidal tract is unsatisfactory. It seemed to Dr. Rhein that the explanation of these movements was the one that he had given above; namely, that the automatic movements were due to the implication of the tract that leads from the lenticular nucleus to the dentate nucleus, and then from this to the inferior olives.

Dr. Charles M. Byrnes said the case was especially interesting in regard to the paresis of the facial nerve and he hoped that Dr. Woods would have more to say about the degree to which the facial nerve was involved. Was the whole nerve at any time completely affected? A recent paper has appeared in the *Revue Neurologique* which explains the escape of the upper part of the face in upper segment lesions of the facial nerve on the belief that the fibers to this portion of the seventh-nerve reach the nucleus by way of the ansa

lenticularis. If this be correct, and if the lesion in Dr. Wood's case is located in the basal ganglions, it would be interesting to know whether the upper facial branch had been involved. Huntingdon's chorea has also been attributed to a lesion in the lenticular nucleus, but Dr. Byrnes did not recall an instance in which this disease has been associated with involvement of the facial nerves. It is, of course, probable that a lenticular lesion might be present in Dr. Woods' case without involvement of this supposed path of the corticonuclear facial fibers.

Dr. William G. Spiller said that the movements in this case were distinctly choreiform. In most of the cases of so-called posthemiplegic chorea the movements are those of athetosis.

In referring to the subject that Dr. Byrnes had brought up, namely, the escape of the upper branch of the facial nerve in central facial palsy, Dr. Spiller said he was observing at that time a case of lethargic encephalitis, which is a form of acute bulbar palsy, and the man had complete loss of power in the lower facial distribution of each side but could close the eyelids of each side. It is well known that in progressive bulbar palsy the upper part of the face is less involved, although the lower part of the face may be completely paralyzed. It is improbable that the nucleus of the upper division of the facial nerve is remote in the brain stem from that of the lower division. Dr. Spiller would attribute this greater escape of the upper branch to the fact that the nucleus of this branch receives much stimulation from both sides of the brain, so that a lesion that might paralyze the nucleus of the lower branch might have less effect on the nucleus of the upper branch, which probably has a greater vitality and is more resistant on account of its double innervation from the cortex. This is not quite the same idea as that employed in the explanation of the escape of the upper branch in supranuclear lesion, when one corticofugal path to the nucleus is affected while the other escapes.

If the nucleus of the upper branch is a part of the general facial nucleus in the pons it must be a distinct group of cells, much as the nucleus of the fibers to the anterior tibial muscle is distinct from that of the fibers to the other muscles in the external popliteal nerve supply. In acute poliomyelitis the anterior tibial muscle may be the only one in the external popliteal supply to escape, or it may be the only one in this supply affected, showing that the nucleus of its nerve supply must be somewhat apart from that of the nucleus of the remaining supply.

Dr. Charles K. Mills said that the case was interesting in connection with the consideration of the cerebral tonectic apparatus and mechanism, a subject to which he had given much attention. In the patient under discussion he thought it probable that the lesion was one of the lenticula, as somewhat similar cases had been reported by von Monakow and others. Years ago, while investigating the pathology of chorea, Flechsig observed small globular bodies on the vessels in the middle and inner zone of the lenticular nucleus. These bodies were supposed by Flechsig and others probably to be the result of calcareous degeneration of some new growth whose nature had not been determined. Dr. Mills believed that both the premotor cortex and the striate body were portions of a cerebral apparatus concerned with maintenance and distribution of tone. One of the special functions of the lenticula seemed to be the rhythmitization of synergic movements differentiated in the cortex and controlled in part by the cerebellum. Such rhythmitization is interfered with in chorea, or at least in certain types of choreic cases.

Dr. Charles S. Potts said that Dr. Rhein had mentioned a case that he had studied pathologically with Dr. Potts. It was so long ago that Dr. Potts did not recall the entire history of the man, but he remembered his movements were very similar to those of the man presented by Dr. Woods.

Dr. A. H. Woods, replying to Dr. Byrnes' question, said that the patient showed no facial weakness, and apparently the facial nerve was not involved at any time. From the paucity of symptoms, one would judge, the lesion was small, so that a tract in or near the claustrum might easily have been spared.

A SPECIMEN FROM A CASE OF CEREBELLAR TUMOR. Presented by Dr. P. G. Hamlin.

History.—A negro, a man, aged 40, was admitted on Oct. 11, 1919, to the Philadelphia Hospital, service of Dr. C. W. Burr. The patient complained of pain in the head, pains throughout the body, soreness and stiffness of joints and dizziness; the onset of his illness was four months previous to his admission to the hospital. He had had a chancre fourteen years ago and had been a daily drinker of whisky. He had had no difficulty in walking until just before coming to the hospital.

Examination.—Station was poor, worse with the eyes shut. The gait was slow and careful, as if in fear. When he was in bed, no ataxia on voluntary movement of the legs was present. There were no cranial nerve palsies. The hearing was poor but had been so for years. The pupils were equal, the right pupil reacted fairly well to light, the left sluggishly; both reacted to accommodation. No nystagmus, no hemianopsia nor disturbance of speech, either paralytic or aphasic were present. In the hands there was no adiadokocinesis. The biceps jerks were normal on both sides, the patellar jerks were exaggerated on both sides. The Achilles jerk was exaggerated on the right, normal on the left. There was no ankle-clonus. Bladder and rectal control were normal. No muscular wasting in arms or legs was present and motor power in both arms was good. Far advanced pulmonary phthisis was found. The mental state was good.

Nov. 7, 1919: The man had lost all motor power in his legs, he could move the arms in all directions, but weakly. A reflex was not brought out on stroking the outer side of the sole but on stroking the inner side there was a slight withdrawl of the foot. Marked intention tremor of both hands with slight tremor of hands at rest was noted. The cremasteric, abdominal and biceps jerks were normal on both sides. There was marked general emaciation of the whole body, but no local muscular atrophy. Rigidity of the neck had developed. Both pupils were dilated, the left was larger; reaction to accommodation was better than to light. Incontinence of the bladder and rectum was complicating the scene. At the beginning of an examination he answered well, but in a few minutes he became confused.

On admission, the temperature was normal. Two weeks later it rose to 100 F. From then until death it ran from 101 to 102 and immediately before death it rose to 106.2 F.

During his stay in the hospital he complained constantly of headache, especially over the right eye. He had not vomited and complained little of vertigo.

Blood Wassermann: Cholesterin, ++++; acetone, ++; syphilitic liver, ++. The spinal fluid Wassermann test was negative. Cytologic examina-

tion of the spinal fluid showed 250 cells per c.c. The percentage of large lymphocytes and polynuclears was equal. Endothelial cells were present; no bacteria.

Necropsy.—On the under surface of the right lobe of the cerebellum a tumor mass about 4 cm. in diameter was observed. Over the mass the dura was densely adherent. The tumor was flattened out from above downward, well outlined, and dense. Much of the cerebellar substance was encroached on where the tumor mass fitted in. The cerebellopontile angle was not invaded by the growth. Subsequent histologic study of the tumor and staining for spirochetes by the method of Levaditi led to the diagnosis of tuberculoma. The slides were studied by Dr. Baxter L. Crawford and the diagnosis was concurred in by Drs. Coplin and Rosenberger.

Complete Pathologic Diagnoses: Tuberculoma of the right lobe of the cerebellum; extensive bilateral tuberculosis with multiple cavity formation of the left lung; tuberculous lymphadenitis, mesenteric; emphysema, right lung. The heart showed myocardial degeneration and the kidneys moderate acute diffuse nephritis. Chronic adhesive bilateral pleuritis was present.

One interesting feature in this case is that the tuberculous condition so masked the cerebellar manifestations that the presence of the cerebellar new growth was not recognized during life; in fact, tumor was not thought of. Exact diagnosis would in any event have been impossible. The mental state was probably due to the general infection. It, of course, was not caused by the tumor. Another interesting feature is the concurrence of syphilis and tuberculosis. Circumstances prevented a fundus examination, and the condition of the optic nerve head is therefore unknown.

LANTERN DEMONSTRATION OF INTRACRANIAL FOREIGN BODIES. Presented by Dr. Samuel D. Ingham.

Dr. Ingham gave a lantern demonstration illustrating the radiographs of a series of cases of intracerebral foreign bodies occurring among the soldiers with head wounds who were under observation at U. S. Army General Hospital No. 11, Cape May, N. J., from October, 1918, to July, 1919. Radiographs were made as a routine measure in all cases of gunshot wounds of the head, from exposure both in the anterior, posterior and the lateral aspects of the cranium. This means practically insured detection of foreign bodies, and determined with a fair degree of accuracy their location as well as the point at which each penetrated the skull. These cases were of neurologic interest on account of the focal cerebral symptoms manifested, and also as illustrations of the great tolerance of the brain to the presence of foreign bodies within it. The salient clinical aspects of the cases illustrated were briefly outlined, and the point of entrance, course and position of the foreign body in each case demonstrated. It was considered, however, that cases of this type were not particularly favorable for the study of cerebral localization because of the wide extent of the lesions usually produced by the deep penetration of the foreign bodies.

Among 200 cases of head wounds the presence of intracerebral metallic foreign bodies was determined in twenty-three, and the cases illustrated were representative of the group.

It was noted with interest that the presence of foreign bodies within the brain did not appear to cause any symptoms, with the one exception in which jacksonian attacks were evidently related to the presence of a small piece of shell just beneath the motor cortex. There was no evidence in any case that

a foreign body within the brain changed its position through the influence of gravity, and no late abscesses of the brain developed as might have been expected as the result of infection being carried deep into the substance of the brain. This type of case was, however, treated with much respect by the surgeons, and it was the rule not to operate for the repair of cranial defects on patients with intracranial defects.

DISCUSSION

Dr. William G. Spiller said that two of the cases reported by Dr. Ingham were particularly interesting, those in which the wound of entrance was in the frontal bone. In one of these cases the man was unable to find his way about. Dr. Ingham did not speak of the loss of orientation in the other case. Dr. Spiller said he was interested in this subject, because Marie and Béhague recently had reported the loss of orientation in space but not in time resulting from a lesion of the frontal lobe. Dr. Spiller had not been able to establish the correctness of the interpretation. He had had a patient with left frontal lobe cyst resulting from a fracture of the skull and that man traveled fifteen miles alone to Camden after he had been injured. This was a clear indication that he had not lost the orientation in space.

Dr. Ingham said that of the entire series of head wounds observed at Cape May there had been a number that showed mental deterioration, and those in which the dementia was most marked had lesions involving both cervical hemispheres. The case about which Dr. Spiller inquired was the only one in which there was a definite disorientation for place, but other symptoms were also prominent; for instance, loss of memory was such that the patient did not remember having been in France. The lesion in this case involved the right frontal lobe and extended diagonally backward and across to the posterior part of the left parietal lobe. In three other cases with dementia the lesions involved both frontal lobes; in two of these the mental symptoms closely simulated paresis. In contrast to these patients having bilateral cerebral lesions were many other cases of unilateral wounds with extensive loss of brain tissue from all the different parts of the cerebrum, including the frontal areas, but which presented no definite evidences of mental deterioration. In Dr. Ingham's experience he had not been able to formulate any definite idea as to the cerebral localization of psychologic symptoms. Bilateral cerebral lesions, however, and especially those involving the frontal lobes, appeared to cause much greater mental disturbance than wounds of similar size affecting only one hemisphere.

Book Review

KOMPENDIUM DER TOPISCHEN GEHIRN UND RUECKENMARKS-DIAGNOSTIK. KURZGEFASTE ANLEITUNG ZUR KLINISCHEN LOKALISATION DER ERKRANKUNGEN UND VERLETZUNGEN DER NERVENZENTREN. Robert Bing, a. o. Professor an der Universität Basel. Vierte, neu durchgesehene Auflage. Mit 97 zum Teil mehrfarbigen Abbildungen.

In his preface to the first edition (1909) the author states that his aim is to present a terse, practical vade mecum for the general practitioner and surgeon who may turn to it when confronted with the task of localizing some pathologic process of the central nervous system. He also undertakes to simplify what is generally considered a complicated domain.

That one untrained in neurology could make any desired localization with the assistance of this book, may well be questioned; but the author has done his work well. Except for considerable diffuseness of style, a sort of conversational excess apparently carried over from the class room, it is hard to see how he could have got more into the 222 pages of text. The subject is treated methodically, and the sequence is quite as logical as necessary conditions permit.

First, there is a sketch of the structural anatomy of the cord, followed by an outline of the essentials of cord physiology. Then are considered seriatim the symptoms indicating involvement of the lateral columns (pyramidal tracts), the anterior horns, posterior roots, posterior horns, etc. Next are taken up the symptoms of a transverse lesion at different levels and of hemisection. This is followed by a detailed presentation of motor, sensory and reflex innervation from different cord segments, which is especially comprehensive as regards the muscles.

Chapter 3 takes up the symptom-groups of high and of low cord lesions and should enable even the neophyte to distinguish one from the other. Eighty-seven pages, about two fifths of the text, are devoted to the spinal cord, the remainder to the brain. Peripheral nerves are not considered.

Consideration of the topographic diagnosis of brain lesions begins with sixty-eight pages on the brain stem (medulla, pons, crura). It includes structure and physiology, and symptoms of lesions of this complicated region, including the cranial nerves. Nothing of importance is omitted; the conclusions are in general sound and the matter is presented about as clearly as could be done within the limits set by the author.

Lesions of the cerebellum include seventeen pages. On this somewhat uncertain ground the author is perhaps a bit too sure; a few statements are to be taken with a grain of salt. But the essentials of cerebellar diagnosis are well outlined and the remarks on vertigo and nystagmus will be helpful to those not neurologically trained.

The final fifty-three pages contain an outline of such cerebral anatomy and physiology as are directly applicable in clinical diagnosis: the general

meaning of the principal sensory and motor signs; the localizing significance of the various central disturbances of vision, speech, hearing, smell, intelligence and character.

Obviously, this book is the result of a great deal of honest, earnest work. It contains an enormous amount of information, and if the author had the gift of clear, succinct statement, it would be almost without fault.

The illustrations are good because they are clearly indicative and therefore helpful. They might be increased with benefit to the beginner, especially in the section on brain stem. Especially do we commend the diagrams of transverse sections of the extremities. The index is not of the best, but it is good.
